Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

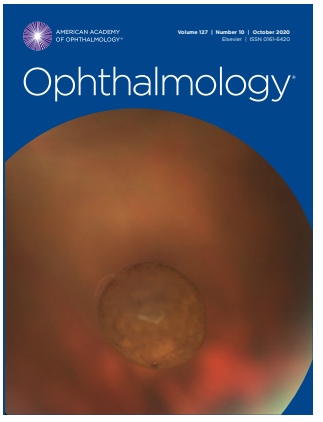
Quarterly Abicipar Is Not Inferior to Monthly Ranibizumab

October 2020

Abicipar is a designed ankyrin-repeat protein that binds VEGF with higher affinity and longer intraocular persistence than ranibizumab. **Kunimoto et al.** compared abicipar administered every eight or 12 weeks to ranibizumab given at four-week intervals in patients with treatment-naive neovascular age-related macular degeneration (AMD). The treatments were comparable in terms of vision stability; however, the rate of intraocular inflammation was higher with abicipar.

For their study, the authors pooled 52-week results of two randomized phase 3 trials (CEDAR and SEQUOIA), which had identical protocols. Patients (n = 1,888) had been assigned to one of three groups. The Q8 group received 2 mg of abicipar initially (baseline, week 4, week 8) and every eight weeks thereafter. Similarly, the Q12 group had 2-mg loading doses of abicipar (baseline, week 4, week 12) followed by the same dose at 12-week intervals. The ranibizumab group received standard dosing of 0.5 mg every four weeks.

The main outcome measure was the proportion of patients with stable vision, defined as best-corrected visual acuity (BCVA) decline of less than 15 letters from baseline. Secondary endpoints were mean changes in BCVA and central retinal thickness (CRT). Adverse events were monitored throughout the study.



At week 52, neither abicipar regimen was inferior to ranibizumab in the primary or secondary efficacy measures. The proportion of patients with stable vision was 93.2% in the abicipar Q8 group, 91.3% in the abicipar Q12 group, and 95.8% in the ranibizumab group. Mean BCVA gains from baseline were 7.5, 6.4, and 8.4 letters, respectively. The mean decrease in CRT was similar for all groups. Although the adverse event rates were similar, intraocular inflammation was more common in patients who received abicipar (15% vs. 0.3%). Because of this, study discontinuation and severe vision loss occurred more frequently with abicipar. Modified drug-purification strategies are being explored to reduce the risk of intraocular inflammation with abicipar.

Assessing RNFL Plus GCIPL Improves Detection of Glaucoma Progression

October 2020

Wu et al. considered that progressive thinning of the retinal nerve fiber layer (RNFL) and the ganglion cell inner plexiform layer (GCIPL) may be a more reliable surrogate of glaucoma progression than the thinning of either layer alone. They found that evaluating these layers together helped identify disease progression in eyes that was not captured by looking at either layer separately. Their technique also boosted the ability to detect visual loss.

In this prospective study, the authors monitored 440 eyes of patients with glaucoma and 98 unaffected control eyes at intervals of approximately four months for at least three years. They used swept-source optical coherence tomography (SS-OCT) with a wide field (12×9 mm^2) to measure RNFL thickness over the parapapillary region, GCIPL thickness over the macula, or the thickness of both layers during the same scan. Thinning was determined from serial SS-OCT data by trend-based progression analysis (TPA). False-positive results were defined as thinning detected by TPA in nonglaucomatous control eyes. Anatomic findings were compared with visual field (VF) results over time.

In the glaucoma group, 127 eyes (28.9%) had progressive thinning of the combined RNFL/GCIPL. Only 74 eyes (16.8%) had progression of the RNFL alone, and just 26 eyes (5.9%) had progression of the GCIPL alone. Thinning of either single layer usually was noted later than thinning of the combined RNFL/GCIPL; the median lag time was about four months. With the false-positive rate controlled at 5%,

TPA specificity to detect thinning was 83.7% with the RNFL/GCIPL combo, 94.9% with RNFL only, and 96.9% with GCIPL only. Eyes with thinning of both layers had the greatest risk of visual loss, including "possible" VF progression (hazard ratio [HR], 2.4) and "likely" VF progression (HR, 4.6).

The authors concluded that TPA detection of progressive thinning of the RNFL/GCIPL combo, based on wide-field SS-OCT data, outperformed longitudinal assessment of either layer alone and captured more eyes at risk of visual decline. Analyzing both layers may be worthy of becoming a standard parameter to monitor glaucoma progression, said the authors. They stressed that their findings apply only to TPA of widefield scans and therefore should not be generalized to progression analysis of circumpapillary RNFL thickness or to guided progression analysis of RNFL or GCIPL thickness obtained with cube scans.

SLT May Slow VF Decline Further Than Standard Treatment

October 2020

Although eyedrops that lower intraocular pressure (IOP) are standard care for glaucoma and ocular hypertension, research has shown that selective laser trabeculoplasty (SLT) may be more effective and less costly for IOP reduction. Although it is clear that these laser treatments lower IOP, little is known about their visual field (VF) outcomes compared with drops. **Wright et al.** compared VF findings of drops versus SLT when used as first-line therapy in patients with glaucoma or ocular hypertension and found that VF deterioration was slower with SLT.

This study was a secondary analysis of 688 patients who participated in the randomized Laser in Glaucoma and Ocular Hypertension trial (344 per study arm). Initial treatment was topical drops in 588 eyes and SLT in 590. IOP targets were similar for both groups. VFs were measured for each eye at nine intervals during a 48-month period and were arranged in series (by median length and duration). Progression rates were grouped according to the degree of progression, measured in decibels per year. Log-binomial regression was used to compare the rates and locations of fast or moderate VF progression between the groups. (These degrees of progression represent greater risk of visual loss.) Hierarchical linear models were used to estimate pointwise VF progression rates, and VF data points were translated into overall global progression estimates for each eye.

There were two main outcome measures: 1) total deviation (TD), reflecting the difference in measured sensitivity at each location from that expected for age and absent pathologic features, and 2) pattern deviation (PD), denoting the TD at each location, adjusted for generalized depression of sensitivity across the VF.

Results of the analysis showed that more patients who received eyedrops had fast or moderate TD progression (26.2% vs. 16.9% in the SLT group). Point-based findings were similar (26.1% vs. 19.0%, respectively). The proportion of PD rates classified as moderate or fast was higher with eyedrops (11.5% vs. 8.3%). More drops-treated eyes had fast or moderate VF decline, but the difference between the groups was not significant.

To slow VF decline, SLT may be the superior first-line treatment for glaucoma or ocular hypertension, the authors said. They advocated incorporating VF outcomes into trials of new treatments for glaucoma and ocular hypertension, versus focusing solely on IOP.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Exercise Intensity and Glaucoma

October 2020

As the impact of exercise intensity on glaucoma has been poorly understood, **Tseng et al.** set out to examine this issue in the National Health and Nutrition Examination Survey (NHANES) population. They found that increased exercise intensity is associated with decreased odds of glaucoma.

For this retrospective cross-sectional study, the researchers evaluated adult participants (age 40 and older) of the 2005-2006 NHANES. Exercise intensity was assessed via objective and subjective measures (accelerometer readings and questionnaire responses, respectively). Glaucoma was characterized with two definitions, based on 1) the Rotterdam criteria and on 2) an ophthalmologist's grading of optic disc photos. Logistic regression was performed to assess associations between exercise intensity and glaucoma while controlling for covariates; the latter included age, gender, ethnicity, blood pressure, body mass index, and spherical equivalent.

The study included a sample of 1,387 NHANES participants; of these, 68 (4.9%) had glaucoma based on Rotterdam criteria, while seven (0.5%) had glaucoma based on image grading. After adjusting for covariates, each 10-count increase in accelerometer intensity was associated with a 5% to 10% decreased adjusted odds of glaucoma.

With regard to subjective reporting of exercise, when the Rotterdam criteria were used, participants who reported that they spent more of the day standing or walking had a 58% decreased adjusted odds of glaucoma than did those who spent more of the day sitting. In addition, when graded disc images were used, those who reported moderate levels of vigorous activity had a 95% decreased prevalence of glaucoma compared to those who reported no vigorous activity.

This study is limited by its observational nature, the authors noted. Further population-based studies of associations between different aspects of exercise and the development or progression of glaucoma are warranted.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Cilioretinal Arteries and Macular Vasculature in Highly Myopic Eyes

October 2020

Using optical coherence tomography angiography (OCTA), **Zhu et al.** set out to evaluate cilioretinal arteries and the

macular vasculature in highly myopic eyes. They found that the presence of cilioretinal arteries in these eyes may improve the macular vasculature and influence visual function.

For this retrospective observational case series, the authors evaluated 481 patients with high myopia (481 eyes) in the Shanghai High Myopia Study database. They compared vessel density, fractal dimension, and foveal avascular zone in OCTA images of eyes with and without cilioretinal arteries between the two groups. Vessel distribution and visual acuity (VA) also were assessed. Main outcome measures were cilioretinal arteries, macular vasculature, and their associations.

All told, 82 eyes (17.05%) had a cilioretinal artery. These eyes had significantly higher vessel density values, higher fractal dimension values for both the superficial and deep vascular plexuses, and a significantly smaller foveal avascular zone than did eyes without cilioretinal arteries. However, these differences were not found in the subgroup of eyes with an axial length of more than 30 mm. Best-corrected VA was better in eyes with cilioretinal arteries than in those without (0.09 ± 0.14 logMAR vs. 0.21 ± 0.27 logMAR, respectively). This was particularly true in eyes in which the cilioretinal artery reached the central foveal area.

This constellation of findings suggests that "the volume of the macular vasculature and the complexity of vascular branching in both the superficial and deep capillary layers were improved by the additional perfusion to the macula from the cilioretinal artery," the authors wrote. With regard to the lessened impact in eyes with longer axial lengths, they suggested that the cilioretinal artery in these eyes is stretched and distorted and, as a result, is unable to provide sufficient additional perfusion.

The authors also noted that some features can confound VA results, including the presence of cataracts and age-related macular degeneration. Thus, additional studies are needed to tease out the potential protective effect of the cilioretinal artery in highly myopic eyes. —*Summary by Jean Shaw*

JAMA Ophthalmology

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

Are Ophthalmology Practices Following COVID Guidance for Patient Visits?

September 2020

On March 18, 2020, the Academy recommended that all ophthalmologists provide only urgent and emergency care, as determined by their judgment. **Starr et al.** assessed whether comprehensive ophthalmology practices in the United States followed this guidance and found that most providers had complied. Before scheduling urgent visits, all practices were likely to ask patients about COVID-19 symptoms.

For this study, the investigators placed scripted phone calls on April 29 and 30 to private practices (n = 40) and university centers (n = 20) that were chosen randomly. The calls represented patient requests for three clinical scenarios: refraction, cataract evaluation, and symptoms of posterior vitreous detachment (PVD). Responses to the requests were compared regionally and between private practices and university centers. The main outcome measure was time to next appointment for each scenario. Secondary measures included use of telemedicine and emphasis of COVID-19 precautions.

Of the 40 private practices, two (5%) were closed, 24 (60%) were seeing only patients with urgent needs, and 14 (35%) were open to all patients. Of the 20 university centers, two (10%) were closed, 17 (85%) were open just for urgent care, and one (5%) was open for all patients. University centers were more likely than private practices to require precautions to limit spread of the virus (85% vs. 35%). The next available appointment for cataract assessment was earlier for private practices (mean, 22.1 vs. 75.5 days). Private entities also were more likely than university centers to continue seeing patients with flashes and floaters (75% vs. 40%), which can signal PVD. The only regional difference was that practices in the South scheduled cataract consults earlier than did practices elsewhere. The responses of centers in areas of higher COVID prevalence were similar to those in areas of lower prevalence. Less than 20% of practices were offering telemedicine.

Extended-Interval Faricimab Versus Monthly Ranibizumab

September 2020

Faricimab, a bispecific antibody for intraocular use, has been proven as safe and effective as ranibizumab in neovascular age-related macular degeneration (AMD) when given every four or eight weeks. This led **Khanani et al.** to investigate whether the maintenance interval for faricimab could be extended up to 16 weeks without sacrificing vision gains obtained on average before extension. They found that vision and anatomic improvements were maintained through follow-up and appeared comparable to those achieved with monthly ranibizumab.

For this phase 2 trial, the researchers included 76 patients (mean age, 78.5 years) who had treatment-naive choroidal neovascularization related to AMD. The study participants' best-corrected visual acuity (BCVA) ranged from a letter score of 73 (approximately 20/40) to 24 (approximately 20/320). Participants were assigned randomly (1:2:2) to receive intravitreal ranibizumab (0.5 mg) every four weeks or faricimab (6.0 mg) every 12 or 16 weeks following four consecutive injections of faricimab every four weeks. Rescue injections were not permitted.

Both faricimab groups received monthly treatment for the initial four months, after which the dosing intervals were extended in the faricimab groups. Patients in the 16-week group were checked for disease activity at week 24. Those without active disease continued on the same schedule through week 52, and those with disease activity had their dosing interval shortened to 12 weeks. Study medication was given up to week 48, and the final visit was at week 52. The main outcome measure was change in BCVA from baseline to week 40. Secondary endpoints included safety findings, monthly changes in BCVA,

and anatomic changes from baseline to weeks 40 and 52.

At week 24, which was 12 weeks after the final loading-dose injection, 36 (65%) of the 55 faricimab recipients had no disease activity. At week 40, the adjusted mean gains in BCVA from baseline were 11.4 for the ranibizumab group, 9.3 for the 12-week faricimab group, and 12.5 for the 16-week faricimab group. The mean (standard deviation) total number of injections from baseline to week 52 was 12.9 (0.25), 6.7 (0.91), and 6.2 (0.93), respectively. Secondary BCVA and anatomic outcomes for faricimab resembled those for the primary end point and appeared comparable to findings for ranibizumab. No new safety concerns arose. *(Also see related commentary by Irina De La Huerta, MD, PhD, Stephen J. Kim, MD, and Paul Sternberg Jr., MD, in the same issue.)*

Triaging Glaucoma Appointments Amid the Pandemic

September 2020

During the pandemic, professionals caring for patients with sight-threatening diseases must decide whether some patients' appointments can be safely postponed. Another challenge is prioritization of rescheduled appointments. **Bommakanti et al.** developed a flexible and scalable scoring system for patients with glaucoma that accounts for disease severity and progression risk, as well as risk factors for COVID-related morbidity. This "big data" tool proved useful for determining which appointments could be delayed and for establishing an appropriate rescheduling scheme.

For this cross-sectional study, the authors identified patients with clinic appointments that had been scheduled from mid-March to mid-April 2020 at an academic center enrolled in the Sight Outcomes Research Collaborative Ophthalmology Electronic Health Record Data Repository. This information was used to create a system that involved scoring glaucoma severity and progression risk as well as COVID morbidity risk. High-risk factors for COVID-related morbidity or mortality included being older than age 65, chronic comorbid medical illness, and pregnancy. The two scores were summed for each patient. The total value helped determine whether to keep or postpone the visit, and it guided the prioritization of rescheduled appointments.

Overall, 1,034 adults with appointments scheduled for that month were eligible for inclusion. Their glaucoma severity and progression risk scores ranged from –50 to 20 (mean, 4.0). COVID morbidity risk scores ranged from 0 to 55 (mean, 27.2). Total scores ranged from –50 to 75 (mean, 31.2). To translate these data into actionable items for clinicians, the authors determined the percentage of visits that could safely be postponed based on score thresholds of 0, 25, and 50 points. This strategy identified 970 (93.8%), 668 (64.6%), and 275 appointments (26.6%), respectively, that could be rescheduled.

—Summaries by Lynda Seminara

American Journal of Ophthalmology

Selected by Richard K Parrish II, MD

Trends in the U.S. Eye Care Workforce

October 2020

In response to predictions that ophthalmology will have the largest workforce shortage among surgical specialties by 2025, **Feng et al.** gathered data from the 2017 Area Health Resources File to explore temporal and geographic personnel trends in recent years. They found that the proportion of ophthalmologists has decreased in the past two decades, while that of optometrists has increased. Moreover, rural areas continue to have disproportionately fewer eye care provides than do other areas.

Outcome measures of the study included the density of practicing ophthalmologists and optometrists per 100,000 individuals, on a county level. The counties were classified as metropolitan, nonmetropolitan, or rural, and various characteristics of their populations were documented. Ophthalmologists also were classified by age group (e.g., older or younger than 55).

From 1995 to 2017, the density of ophthalmologists in the United States declined from 6.30 to 5.68 per 100,000 individuals. For optometrists, density grew from 11.06 in 1990 to 16.16 per 100,000 individuals in 2017. Although the density of ophthalmologists in rural counties increased 2.26% from 1995 to 2017, the density in those counties was significantly lower (0.58) than in nonmetropolitan (2.19) or metropolitan areas (6.29). The ratio of older (>55 years) to younger (<55 years) ophthalmologists rose from 0.37 in 1995 to 0.82 in 2017, with the greatest ratio increase—from 0.29 to 1.90—taking place in rural counties.

The authors suggested several potential reasons for the disparity of available ophthalmologists in rural counties, including insufficient health care infrastructure.

Slit-Lamp Breath Shields Provide Some Protection From COVID-19

October 2020

Liu et al. assessed the capability of seven slit-lamp breath shields in preventing droplet overspray from a simulated sneeze. They found varying degrees of effectiveness among the tested shields, with the quantity of overspray ranging from 0.3% to 54% of the dispersion amount.

For their study, a dimensionally accurate slit-lamp model was constructed from cardboard, and the nozzle of a spray gun was adjusted to disperse a mist of colored dye that approximated a sneeze. Five popular commercial breath shields were purchased. Another was created from cardboard and simulated the size and shape of a sixth commercial shield. The seventh shield was a salad container lid with edges that curved toward the examiner. Surface area of the breath shields ranged from 116 to 1,254 cm^2.

The cardboard slit-lamp model was sprayed without a breath shield in place to establish the control area of spray. Each shield was placed on the objective lens arm or was hung from the oculars. The shields were sprayed three times each, in a standardized fashion, using a fresh sheet of white poster paper placed directly behind the oculars. Areas of spray were photographed, quantified,

and averaged. The amount of overspray was compared with the unshielded (control) quantity of spray.

Shields attached to the objective lens arm prevented more spray than those hung by the oculars. Moreover, with one exception, larger shields performed better than smaller ones. The best-performing conventional commercial shield was the cardboard-simulated "Zombie Shield," which was hung near the oculars; it allowed only 0.3% of the spray to reach the poster paper.

A disadvantage of larger shields is their tendency to impede access to slit-lamp controls. Another factor affecting performance is the shape of the shield. The plastic lid, although not large in surface area (513.1 cm^2), was more effective than five of the six commercial shields. The authors noted that even high-functioning shields should be used with other personal protective equipment. They emphasized that patients should wear a mask and avoid speaking during slit-lamp exams.

—Summaries by Lynda Seminara

Other Journals

Selected by Prem S. Subramanian, MD, PhD

HbA1c Modifies Genetic Susceptibility to Severe DR

Investigative Ophthalmology & Visual Science
2020;61(10):7.

Studies of the effect of glycemic control on genetic susceptibility to severe diabetic retinopathy (DR) in type 2 diabetes are limited. **Ng et al.** expanded on a previous case-control study and found a possible link between the single-nucleotide polymorphism (SNP) *COL5A1* rs59126004 and the risk of severe DR, as well as data suggesting that hemoglobin A1c (HbA1c) can modify this genetic susceptibility.

For this study, the researchers evaluated 3,093 Southern Chinese patients with type 2 diabetes. Of these, 2,042 served as controls, and 1,051 had sight-threatening DR. A subset of those with DR (n = 409) had proliferative DR (PDR). Sixty-nine SNPs from previous genome-wide association studies were investigated for a potential relationship with severe DR (subgroup analysis). SNPs that showed possible associations were examined by HbA1c value (<7% vs. ≥7%; stratified analysis) and in a multiple logistic regression model (interaction analysis).

Results showed that patients with sight-threatening DR had longer duration of diabetes, higher HbA1c levels, and greater likelihood of hypertension. After adjustment for traditional risk factors, four SNPs were nominally linked to sight-threatening DR. In the stratified analysis, HbA1c <7% was associated with a 42% lower risk of sight-threatening disease per additional protective C allele of *COL5A1* rs59126004 ($p = 1.76 \times 10^{-4}$; odds ratio [OR], 0.58). This effect was not observed with HbA1c ≥7%. In the subgroup analysis for PDR, *COL5A1* rs59126004 produced an even stronger protective effect: 63% lower risk of sight-threatening DR per additional C allele ($p = 8.35 \times 10^{-5}$; OR, 0.37). In the gene-environment interaction analysis, *COL5A1* rs59126004 showed significant interactions with dichotomized HbA1c on both sight-threatening disease and PDR risk. No other SNP showed significance in the interaction analysis.

Although *COL5A1* rs59126004 had a favorable modifying effect on sight-threatening DR and PDR in this study, the authors cautioned that their results are based on a one-time HbA1c measurement rather than a patient's mean HbA1c throughout the course of diabetes.

Nonetheless, this study adds evidence to support the effect of tight glycemic control in DR prevention.

Novel Device for Rapid Triage of Glaucoma Patients

British Journal of Ophthalmology
Published online Aug. 3, 2020

Jones et al. previously found that an eye-tracking device provided visual field (VF) data comparable to that of standard automated perimetry (SAP). They followed up on these initial results by investigating whether this open-source device, known as Eyecatcher, could identify patients with pronounced VF loss (mean deviation [MD] worse than –6 dB in at least one eye) and flag false-positive referrals (MD > –2 dB) in the waiting room of a busy glaucoma clinic. They found that Eyecatcher may be a quick and convenient complement to SAP.

In this study, adults on a routine visit to a U.K. glaucoma clinic were instructed to sit 55 cm from a Windows Surface Pro 4 tablet and look at anything they saw on it. Targets of varying intensity were displayed, and a clip-on eye tracker determined which targets were noticed. The test was done twice in the same eye. Participants answered a five-item questionnaire about Eyecatcher and conventional SAP (performed later in the same visit).

The 77 enrollees included returning patients with established glaucoma and new false-positive referrals (with no measurable VF loss or optic nerve abnormalities). Sixty-nine patients completed the study. Accuracy between Eyecatcher (mean hit rate) and SAP (MD) based on 11 new referrals and 11 randomly selected follow-up patients was consistent (Spearman correlation, $r = 0.78$; $p < .001$). Eyecatcher had good capability to distinguish MD less than –6 dB from MD greater than –2 dB (area under the receiver operating curve, 0.97). Moreover, Eyecatcher flagged 68% of false-positive referrals as functionally normal and labeled no patients with substantial VF loss as visually normal. However, some patients with a healthy VF scored poorly. Eyecatcher was faster than SAP, and participants considered it more enjoyable and easier to perform (both $p < .001$). SAP had better test-retest reliability and tested more locations.

Eyecatcher shows potential to prioritize patients at busy clinics and could prevent unnecessary patient visits if used in a comprehensive ophthalmology setting. It also may be ideal for home monitoring and for people with limited physical or cognitive ability, the authors said. They cautioned that the device cannot test central vision and, without improvements, would be a poor general screening tool if both high sensitivity and high specificity are required.

—Summaries by Lynda Seminara