Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

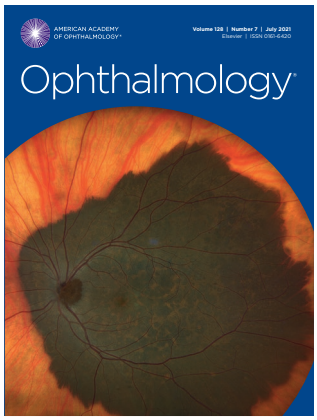
Abicipar for Neovascular AMD: Two-Year Results

July 2021

Khurana et al. pooled two-year data for the CEDAR and SEQUOIA trials and found that abicipar was effective when given every eight or 12 weeks (Q8 or Q12) for neovascular age-related macular degeneration (AMD). This longer duration of effect, when compared to ranibizumab, translates to fewer overall injections and lower costs for patients with neovascular AMD. However, a higher incidence of intraocular inflammation was noted in abicipar-treated eyes than in those that received ranibizumab.

The CEDAR and SEQUOIA trials were designed to test whether abicipar is noninferior to ranibizumab through 52 weeks in patients with active choroidal neovascularization secondary to AMD. One eye per patient was enrolled; best-corrected visual acuity (BCVA) ranged from 24 to 73 ETDRS letters. Favorable results led to treatment continuity through week 104 to determine if the benefits persisted for another year. In year 2, each patient received four or six injections of abicipar or 11 injections of ranibizumab. Efficacy measures included stable vision (a loss of <15 letters from initial baseline values) and changes in central retinal thickness (CRT). Adverse events were recorded to assess safety.

The final analysis set included 443 patients on abicipar Q8, 442 on abicipar Q12, and 520 on ranibizumab Q4. At week 104, vision was stable in 93.0%, 89.8%, and 94.4% of those in each cohort, respectively. Mean BCVA gains from baseline were 7.8, 6.1, and 8.5 letters, respectively. Mean CRT reductions from baseline were 147 µm, 146 µm, and 142 µm, respectively.



With regard to intraocular inflammation, the overall incidence of inflammation from baseline through week 52 was 15.4% for the abicipar Q8 patients, 15.3% for those who received abicipar Q12, and 0.3% of those who received ranibizumab Q4. From baseline through week 104, those percentages were 16.2%, 17.6%, and 1.3%, respectively. The overall percentage of enrolled patients who completed the two-year study was 70.8% for the abicipar Q8 cohort, 70.7% for those who received abicipar Q12, and 82.7% for those who received ranibizumab Q4.

Risk of Adverse Ocular Events With Brolucizumab

July 2021

Monés et al. conducted an independent safety review of HAWK and HARRIER data to learn more about investigator-reported cases of intraocular inflammation, endophthalmitis, and retinal arterial occlusion. This analysis was prompted by postmarketing evidence received by the drug's manufacturer indicating that retinal vasculitis or retinal vascular occlusion occurred in up to 4.71 of every 10,000 injections of brolucizumab. The safety committee reported signs of retinal vasculitis, with or without retinal vascular occlusion, which were linked to greater risk of visual acuity (VA) decline. This knowledge should help physicians weigh the risks and benefits of brolucizumab for their patients with neovascular age-related macular degeneration (AMD), said the authors.

Patients enrolled in HAWK and HARRIER had untreated active choroidal neovascularization due to AMD and were assigned randomly to receive brolucizumab or aflibercept. The independent safety review committee studied the subset of cases of intraocular inflammation that occurred (60/1,088 with brolucizumab, vs. 8/729 with aflibercept) by looking at patient data and imaging studies. Main outcome measures were signs and incidence of VA loss and vasculitis and/or retinal vascular occlusion; time from the initial brolucizumab injection to onset of intraocular inflammation; and frequency of VA loss after brolucizumab injection by time of inflammation onset.

In 50 brolucizumab-treated eyes, the intraocular inflammation was definitely

or probably related to the study drug, the safety review committee confirmed. The combined rate of definite/probable inflammation was 4.6%, and eight eyes treated with brolucizumab (0.74% overall) had moderate or severe VA loss. In contrast, the incidence of intraocular inflammation among aflibercept-treated eyes was 1.1%, and moderate or severe VA loss occurred in 0.14%.

The authors encourage close surveillance of patients on brolucizumab therapy to ensure prompt recognition of intraocular inflammation, retinal vasculitis, or retinal occlusion. They recommend adding slit-lamp examinations, ophthalmoscopy, and fundus imaging to the monitoring protocol.

Corneal Stiffness Metrics Signal Glaucoma Progression

July 2021

Qassim et al. assessed whether corneal stiffness metrics could signal risk of progression in eyes suspected of having glaucoma. They found that progression risk was greatest for eyes with relatively high corneal stiffness and low central corneal thickness (CCT). Hence, corneal stiffness parameters (SPs) and CCT may contribute synergistically to progression, they concluded.

For this prospective longitudinal study, the researchers included 371 eyes (228 patients) whose optic disc appearance suggested glaucoma—but whose Humphrey visual field (HVF) results were normal. The researchers obtained corneal SPs at baseline and then assessed patients every six months with clinical examinations, OCT scans, and HVF testing. The baseline SP at first applanation (SP-A1) and highest concavity point predicted the outcome measures. Structural progression was determined by OCT-measured thinning of the retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer (GCIPL). Functional progression was established by permutation analysis of pointwise linear regression criteria on HVF testing.

The authors found a strong correlation between SPs and CCT. A higher SP-A1 value (suggesting a stiffer cornea) signaled faster RNFL thinning ($p < .001$) and thinner CCT ($p = .004$) in the follow-up period, which averaged 4.2 years. Eyes with higher SP-A1 and thinner CCT showed accelerated RNFL thinning (0.72 µm/year) relative to eyes with lower values for these metrics. They also were nearly three times more likely to have RNFL decline exceeding 1 µm/year. Findings for GCIPL thinning were similar. High SP-A1 values also were linked to greater risk of visual field progression ($p = .002$) and thinner CCT ($p = .010$). The risk of visual field decline was 3.7 times greater for eyes with worse SP-A1 and CCT data.

These findings augment the body of evidence denoting the importance of considering corneal biomechanics when estimating progression for eyes with suspected glaucoma.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Machine Learning Predicts Anti-VEGF Treatment Demand

July 2021

Gallardo et al. assessed the potential of machine learning to predict low and high treatment demand in patients with neovascular age-related macular degeneration (AMD) or retinal vascular disease who received treat-and-extend injections in a routine clinical setting. They found that machine learning can predict treatment demand and potentially could be used to establish patient-specific treatment plans.

For this retrospective cohort study, the researchers evaluated 340 patients (377 eyes) with neovascular AMD and 285 patients (333 eyes) with retinal vascular disease. The latter group comprised 150 patients with retinal vascular occlusion (RVO) and 135 patients with diabetic macular edema (DME). All eyes were treated with either aflibercept or ranibizumab according to a predefined treat-and-extend protocol at the University of Bern, Switzerland. The study period ran from 2014 to 2018, and patients received anti-VEGF injections for at least one year.

The researchers defined eyes as low-, moderate-, or high-treatment demanders, using the average interval between treatments (low: ≥10 weeks; high: ≤5 weeks; moderate: all other eyes). They then trained two random forest models to predict the long-term treatment demand of a new patient. Both models used patient demographic information and morphological features automatically extracted from OCT volumes at baseline and after two consecutive visits. Mean area under the curve (AUC) of both models was measured.

In the cohort of patients with AMD, the researchers identified 127 low-, 42 high-, and 208 moderate-treatment demanders. Of those with RVO or DME, 61 patients were low-, 50 were high-, and 222 were moderate-treatment demanders. For patients with AMD, the mean AUC was 0.79 for both low and high demanders. For those with retinal vascular disease, the mean AUC was 0.76 and 0.78 for low and high demanders, respectively. To predict low treatment demand, only the information derived at baseline was necessary. In contrast, accurate prediction of high treatment demand required additional information from follow-up visits.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Social Work Program Boosts Adherence to Follow-Up Care

July 2021

Can social outreach programs bring effective—and low-cost—vision care to children? In a previous study, **Chung et al.** explored costs and outcomes of the Children's Eye Care Adherence Program (CECAP1), a social work intervention shown to improve adherence to eye care for underserved children in Philadelphia. After analysis of the flagship program, the authors modified it to reduce costs. In their subsequent study, they investigated the effectiveness of the reduced-cost model (CECAP2) and found that, even when costs were lowered by more than 50%, the program was just as successful.

For this CECAP2 study, the authors gathered data from records of children

who needed ophthalmic follow-up after participating in community-based vision screening programs. They modified CECAP1 to prioritize the children who, based on that earlier study, were more likely to complete a follow-up visit. Efforts were made to decrease phone calls and scheduling attempts and to constrict the geographic catchment area for better accessibility. Costs were based on the social workers' time devoted to the program. Effectiveness was expressed as the percentage of patients who completed at least one follow-up visit within the recommended time frame.

Altogether, 462 children were referred to CECAP2 from the vision-screening programs. Of these, 242 (52.4%) completed a recommended follow-up exam. The proportion was nearly identical to that for CECAP1 (52.3%). Children who spoke English at home were more likely to return for follow-up than were children who spoke another language (60.8% vs. 46.8%). In CECAP2, the social workers' time averaged 0.8 hours per patient—significantly less than previously (2.6 hours per patient). The cost per patient was reduced from $77.20 to $32.73.

To the authors' knowledge, this is the first publication of efforts to minimize costs of a social work program aimed at increasing follow-up adherence. Although CECAP2 is more sustainable than CECAP1, the authors do not wish to overlook children who are "lost to follow-up." Rather, they hope other interventions can be developed to reach those children.

PAK Outcomes Are Better for Contact Lens Wearers

July 2021

Pseudomonas aeruginosa is a common cause of bacterial keratitis among patients who wear contact lenses. **Enzor et al.** compared risk factors and outcomes for *P. aeruginosa* keratitis (PAK) between contact lens wearers (CLWs) and those who do not wear contacts. They observed better outcomes among CLWs. Strong predictors of poor visual acuity (VA) in both groups were worse initial VA, advanced age, larger infiltrate or epithelial defect at presentation, and greater maximum depth of stromal necrosis. Stromal necrosis required more than conservative treatment in nearly half of non-CLWs but in less than 14% of CLWs.

For this retrospective study, the authors evaluated 214 eyes with PAK. Of these, 163 were in the CLW cohort. For both groups, the authors assessed patients' clinical features, microbiologic findings, and treatment course. They also conducted analyses based on machine learning to determine predictors of poor final VA.

Patients' average age was 39.2 years for CLWs and 71.9 for non-CLWs. At presentation, mean logMAR VA was 1.39 and 2.17, respectively ($p < .0001$). The mean final VA was 0.76 in CLWs and 1.82 in non-CLWs ($p < .0001$).

Throughout treatment, PAK was more severe in non-CLWs. In addition, the hospitalization rate was significantly higher for this group (58.8% vs. 19.6%): The mean hospital stay was 9.29 days for non-CLWs, versus 5.44 days for CLWs. Stromal necrosis required surgical or procedural intervention in 13.5% of CLWs and 49.0% of non-CLWs ($p < .0001$). According to machine learning analyses, strong predictors of poor VA outcomes (i.e., worse than 20/40) were older age, worse initial VA, larger infiltrate or epithelial defect at presentation, and greater depth of stromal necrosis.

In most published cases of PAK, the condition is linked to contact lens wear because *P. aeruginosa* is the most frequently isolated pathogen from corneal scrapings of patients with infectious keratitis who wear contacts. Although this relationship certainly deserves attention, the authors emphasized that PAK also is a common cause of keratitis in non-CLWs, as shown by their findings. They recommend further study of PAK, particularly to explore reasons for the major differences in outcomes between CLWs and non-CLWs. Although *P. aeruginosa* is more prevalent in CLWs, the related damage seems more severe for non-CLWs, leading to more challenging treatment courses and poorer VA outcomes.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Ethnic Disparities in Clinical Trials of Ophthalmic Drugs

June 2021

Berkowitz et al. evaluated the ethnic representation, trends, and disparities in clinical trials leading to FDA ophthalmology drug approvals from 2000 to 2020. They found that Black, Hispanic, and other non-White populations were underrepresented in these studies, although some improvement occurred during the 20-year time frame.

For this cohort study, the researchers used data from participants in 31 clinical trials of drugs for neovascular age-related macular degeneration (AMD; n = 10), open-angle glaucoma (OAG; n = 16), and expanded indications for diabetic retinopathy (DR; n = 5). All told, 13 drugs were studied.

National expected ethnic proportions were sourced from U.S. Census Bureau and NEI data. The primary outcome measures were the distribution of and change over time in the ethnic proportion of participants in clinical trials leading to FDA approval of drugs for the three disease categories.

The 31 clinical trials involved 18,410 participants. With regard to overall participation, disparity analyses showed overrepresentation of White participants and underrepresentation of Black and Hispanic participants compared with the expected disease burden and ethnic distribution in the United States. These disparities did begin to narrow over time, with increased enrollment of Asian participants in AMD and DR studies, increased participation of Hispanics in AMD and OAG trials, and increased enrollment of Black patients in OAG studies. However, there was no change in enrollment of Black participants in AMD studies and a decrease in Black participants in DR trials.

The researchers noted that category reporting by ethnicity was inconsistent and variable across the studies evaluated, and they called for comprehensive and standardized reporting of demo-

graphic characteristics in clinical trials.

Above all, they said, investigators should focus on diverse, representative enrollment in pivotal studies. *(Also see related commentary by Päivi H. Miskala, MSPH, PhD, and Senaka A. Peter, MPH, in the same issue.)*

Older Drivers and Accidents

June 2021

Swain et al. set out to examine the visual risk factors associated with at-fault crashes and near crashes among older drivers, using data acquired from sensors placed in the drivers' cars. They identified three visual factors likely to increase a driver's risk of accidents and near accidents.

For this study, the researchers evaluated 154 participants 70 years of age or older who reported driving at least four days a week. An unobtrusive data acquisition system, which captured information on roadway environment, accelerator position, brake actuation, and speed, was installed in each participant's car. The participants were instructed to continue their normal driving patterns for six months. The primary outcome was the rate of combined incident at-fault crashes and near crashes, defined by the number of events and the number of miles driven.

Of the drivers, 85 were in their 70s, 66 were in their 80s, and three were in their 90s. Cognitive status was normal in 152 of the participants. Information was available on the eye health of 151 participants; of these, 14 had no eye disease, while the remainder had such conditions as cataract (n = 63; 41.7%), primary open-angle glaucoma (n = 43; 28.5%), age-related macular degeneration (n = 28; 18.5%), and diabetic retinopathy or macular edema (n = 10; 6.6%).

With regard to visual acuity (VA), 151 participants had VA of 20/40 or better, while three had a VA of 20/40 or worse. Seventeen had impaired contrast sensitivity (worse than 1.5 log sensitivity). Visual processing speed was measured in 125 participants; of these, 62 had slowed visual processing speed. Other factors measured included visual field sensitivity and motion perception.

A total of 26 at-fault crashes and 55 at-fault near crashes occurred during the six-month study period. Of these, 55 (67.9%) involved other vehicles. Participants who had deficits in their visual processing speed, contrast sensitivity, and motion perception were more likely to be involved in an at-fault collision or near collision. *(Also see related commentary by Sheila K. West, PhD, in the same issue.)*

PEDIG Report: Lensectomy for Traumatic Cataract

June 2021

The Pediatric Eye Disease Investigator Group (PEDIG) set out to assess visual acuity (VA) outcomes and adverse events in children who undergo surgery for traumatic cataracts. **Bothun et al.** found that, within 15 months after lensectomy in these children, substantial ocular morbidity was common.

This cohort study was drawn from a larger study of 994 children younger than 13 years who underwent lensectomy from June 2012 to July 2015. Traumatic cataract was reported in 84 of the 994 children, and an office visit was documented for 72 of the 84 within 15 months following surgery.

Main outcomes were best-corrected VA (BCVA) from nine to 15 months after lensectomy for traumatic cataract and the cumulative proportion with strabismus, glaucoma, and other ocular complications by 15 months.

For the 72 children (74 eyes), the median age at time of surgery was 7.3 years (range, 0.1-12.6 years), and an intraoperative complication was identified in 10 of the eyes (14%). An IOL was placed in 57 of the 74 eyes (77%). Other results included the following:

- Visual loss was common. In children who were 3 years or older at follow-up, median BCVA was 20/63 for pseudophakic eyes (n = 26; range, 20/20 to 20/200) and 20/250 for eyes with aphakia (n = 6; range, 20/20 to worse than 20/800).
- Visual axis opacification also was common, with a cumulative proportion of 42% among children with IOLs. Most of these patients subsequently underwent laser capsulotomy.
- Data on ocular alignment were available for 64 participants; strabismus was reported in 23 of the 64.
- Glaucoma was infrequent and diagnosed in four of the 74 eyes (all four were pseudophakic). No cases of glaucoma suspect were reported.

Based on these findings, the PEDIG researchers recommended ongoing monitoring of these children, particularly with regard to the development of strabismus and visual axis opacification. *—Summaries by Jean Shaw*

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Stroke Risk Soars After RAO

Eye

Published online April 28, 2021

Based on mounting evidence of a relationship between stroke and retinal artery occlusion (RAO), the American Heart Association recommends immediate assessment for any patient with RAO or amaurosis fugax. Although the Academy has adopted these guidelines, fewer ophthalmologists than neurologists are likely to recommend urgent workup for patients with RAO. **Scoles et al.** assessed the near-term risk of stroke after RAO and found that stroke risk was highest in the days following central or branch RAO.

For this matched-case series, the authors used a large health care claims database and estimated stroke risk for two cohorts: 1) a self-controlled case series (SCCS; n = 16,193) and 2) a cohort matched by propensity score (PS; n = 18,213 with RAO but no previous stroke matched with 18,213 patients with hip fracture). All participants were 55 years of age or older. The date of RAO diagnosis was considered the index date. In the SCCS, stroke incidence was compared for periods before and after the index date. Primary outcome measures were the occurrence of stroke and its timing relative to the index date. Cox proportional regression was applied to determine the hazard ratios for stroke.

RAO raised the risk of stroke in both groups. In the SCCS, the incidence rate

ratio of stroke was significantly higher within 30 days after RAO diagnosis than in periods more than two months before RAO ($p < .012$). In the PS-matched cohort, the hazard ratio for stroke was nearly 3 times greater after central or branch RAO than after hip fracture ($p < .001$).

An unexpected finding of this study was the large number of first strokes occurring shortly before RAO diagnosis. A possible explanation, said the authors, is that a danger period exists in which any embolic phenomenon can occur. Whether or not this proves to be the case, they stressed the importance of promptly referring patients with RAO for a full workup to include stroke evaluation.

Correcting Hyperopia Improves Accommodative Function

Investigative Ophthalmology & Visual Science
2021;62(4):6

Guidelines for optical correction of low to moderate hyperopia in children do not exist, in part because the value of providing correction in this population has not been demonstrated. Although some children can exert adequate accommodation to focus for near work, doing so may be uncomfortable. **Ntodie et al.** looked at the effect of refractive correction on the accommodative responses in children during sustained near tasks and found that correcting low and moderate hyperopia substantially relieved the compensatory efforts.

The authors recruited 134 children between 5 and 10 years of age with varying levels of hyperopia from three settings in the United Kingdom: a local primary school, a community optometric practice, and a university optometry clinic. Of these children, 63 met the inclusion criteria; their spherical equivalent refraction ranged from +1 D to +4.38 D in the less hyperopic eye.

The authors recorded binocular accommodation measures while the children were engaged in reading small print on a Kindle device and watching an animated movie on an LCD screen. The children performed each task for a 15-minute period, both before correction of hyperopia and one week after full correction. The displayed font and font size remained uniform for all reading work. Reading speed was assessed with and without correction. The effect of optical correction on accommodative response was considered "positive" if the correction either improved accuracy of the mean response when there was accommodative lag or reduced the mean response when the accommodative lead was 0.50 D or greater.

Of the 63 qualified enrollees, 62 completed the reading evaluation, and 61 completed the movie portion. After refractive correction, the accuracy of accommodative responses improved for the reading task ($p = .001$) and the movie task ($p < .001$). Reading speed also increased ($p < .001$).

The effects of refractive correction in this study were independent of age or the degree of hyperopia. The authors recommend exploring the longer-term clinical and academic outcomes of hyperopia correction.

—Summaries by Lynda Seminara