

News in Review

COMMENTARY AND PERSPECTIVE

RETINA

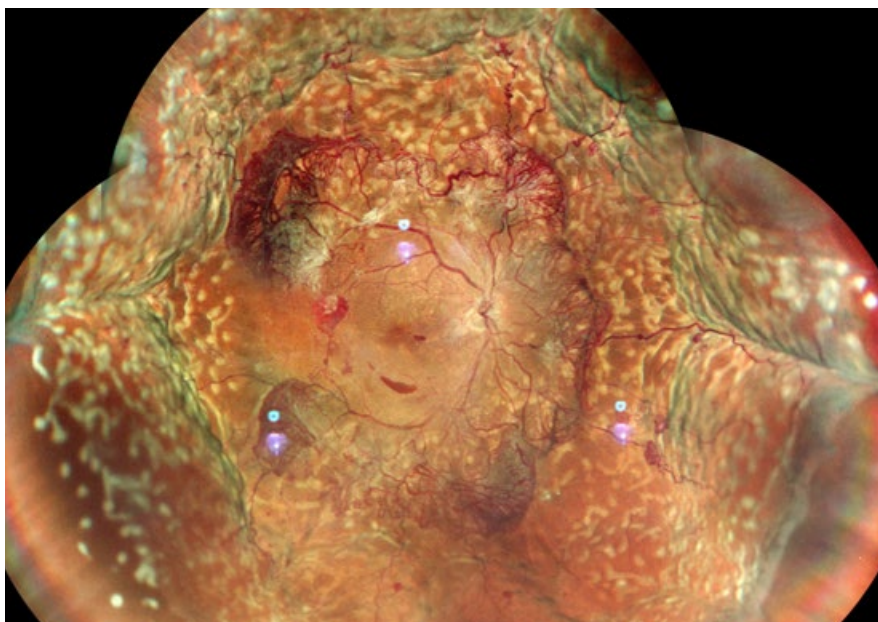
Aflibercept Versus Surgery for Vitreous Hemorrhages

Which treatment is best for vitreous hemorrhages due to proliferative diabetic retinopathy (PDR)? At 24 weeks, intravitreal aflibercept (Eylea) equaled vitrectomy plus panretinal photocoagulation (PRP) in effectiveness, a study from the DRCR Retina Network found.¹

“Vitreous surgery has been the standard treatment for vitreous hemorrhages in patients with PDR since the 1970s. But there was evidence from published small studies showing that intravitreal anti-VEGF therapy was effective in stimulating regression of neovascularization and allowing vitreous blood to clear,” thus potentially reducing the need for surgery, said Andrew N. Antoszyk, MD, protocol chair for the study. “We designed a trial to determine whether medical therapy with intravitreal aflibercept could be a viable first-line alternative to surgery in these eyes.”

The answer: Yes, it is. “Furthermore, neither surgical nor medical treatment had a persistent visual advantage over the other during the two years of follow-up,” said Dr. Antoszyk, who practices in Charlotte, North Carolina.

Study protocol. At 39 sites in the United States and Canada, the researchers randomized 205 patients with monocular, diabetes-related vitreous hem-



ANTI-VEGF CANDIDATE? One week following PRP, this patient with PDR presented with 360-degree choroidal effusion.

orrhages to first-line treatment with either 2-mg injections of aflibercept ($n = 100$) or vitrectomy/PRP. The primary outcome was mean visual acuity (VA) 24 weeks after the initial procedure, with secondary measurements at the one- and two-year marks. Patients could receive the other modality as necessary during the study period.

Outcomes. Four weeks after initial treatment, the mean VA letter score was 52.6 (20/100 Snellen equivalent) in the aflibercept group, versus 62.3 (20/63 Snellen equivalent) in the vitrectomy group ($p = 0.003$). This was an adjusted mean difference of 11.2 letters favoring vitrectomy. However, at 24 weeks, the mean VA letter scores were no longer significantly different, with outcomes of 69.4 letters in the aflibercept eyes, compared to 69.0 in the vitrectomy group (20/40 Snellen for both; $p = 0.88$).

At two years, mean VA remained similar between the two groups but lacked statistical significance: 73.7 let-

ters in aflibercept recipients, versus 71.0 in the vitrectomy group (20/40 Snellen for both; $p = 0.36$).

Number of injections. Patients initially treated with aflibercept required a mean of 8.9 intravitreal injections over two years, and a third of them eventually had to undergo vitrectomy with PRP, Dr. Antoszyk said. “Conversely, a third of the primary vitrectomy group later was treated with aflibercept” and needed only a mean of 2.3 injections, he noted.

Nuances to consider. Improvement in mean VA occurred faster in the primary vitrectomy patients, Dr. Antoszyk said. “At four weeks, there was a 2-line acuity difference [between the two treatments], favoring vitrectomy. That trend began to dissipate as you approached 12 weeks—and this continued until, at 24 weeks, there was just a 0.5 letter difference.”

This pattern suggests that treatment for diabetes-related vitreous hemor-

rhages can safely be guided by each patient's visual needs and preference, without sacrificing longer-term VA, Dr. Antoszyk said. For instance, a patient with poor vision in the contralateral eye might prefer vitrectomy/PRP as primary therapy, in order to regain vision in the treated eye quickly, he said. Conversely, patients averse to undergoing surgery can be treated initially with aflibercept, with the goal of either avoiding surgery or postponing it for as long as possible.

The study also showed that less dense hemorrhages are the likeliest to clear quickly with aflibercept, Dr. Antoszyk said. "If the affected eye has a VA of better than 20/800, that's a subpopulation that recovers more quickly because their hemorrhage is not as dense. They may be able to benefit from intravitreal

injections as their primary therapy."

The findings from the trial are reassuring in a time of potential pandemic-related delays in surgeries, he said. "If patients can't get to the OR, we now know that aflibercept is a great alternative. You would at least be buying them time to stabilize the neovascularization and allow the blood to clear sufficiently," Dr. Antoszyk said. And if their hemorrhages recur, he said, "you know that over this time course, even if you had to delay surgery, you'd still have an excellent visual outcome."

—Linda Roach

1 Antoszyk AN et al. *JAMA*. 2020;324(23):2383-2395.

Relevant financial disclosures—Dr. Antoszyk: Jaeb Center for Health Research: C; Genentech: C,S; Regeneron: C; Roche: C,S.

OCULOMICS

Using OCT and OCTA to Detect Parkinson

First Alzheimer, now Parkinson: A team of researchers has identified several potential retinal and choroidal biomarkers for the diagnosis of Parkinson disease (PD).¹ The team previously used optical coherence tomography (OCT) and OCT angiography (OCTA) to describe retinal changes observed in patients with Alzheimer disease.²

In Parkinson, none of the biomarkers in isolation proved useful enough to boost confidence in making the diagnosis; however, the study underscores the importance of the eye-brain

CORNEA

Comparing CXL Protocols

WHICH OF THE TWO MAIN CORNEAL CROSS-LINKING (CXL) techniques for corneal ectasia is safer and more efficacious? A team of Canadian researchers who waded into this debate came up with mixed results.¹ Their meta-analysis found that while transepithelial CXL is significantly safer than conventional epithelium-off CXL, it remains inferior in its ability to reduce corneal steepness and arrest disease. Nonetheless, the researchers found equivalent visual and refractive outcomes between the two approaches.

"This creates a conundrum, as there is no clear way forward," said Siddharth Nath, MD, PhD, at McGill University in Montreal.

Pros and cons. The researchers identified 12 randomized controlled studies, totaling 966 eyes.

Efficacy. The primary outcome of this meta-analysis was change in maximal keratometry (K_{max}) 12 months following CXL. In the transepithelial group, K_{max} decreased from a preoperative baseline of 52.38 D to 52.32 D, compared to a decrease from 52.80 D to 52.26 D in the epithelium-off group.

In addition, the researchers found that disease progression, defined as an increase of ≥ 1.0 D in K_{max} at 12 months, was significantly higher in transepithelial CXL eyes (7%) than epithelium-off eyes (2%).

Safety. The rate of significant complications (corneal melt, persistent epithelial defects, and visually significant nonresolving haze) was 4% with conventional CXL, versus 2% with transepithelial CXL.

Visual outcomes. No significant differences were observed in changes to corrected and uncorrected visual acuity. In the transepithelial group, uncorrected distance visual acuity (UDVA) improved from 0.85 Log-MAR units at baseline to 0.70 at 12 months following CXL; UDVA in the epithelium-off eyes improved from 0.80 at baseline to 0.64 at 12 months. For corrected distance VA, those pre- and posttreatment measurements were 0.30 and 0.22 in transepithelial eyes and 0.28 and 0.18 in the epithelium-off group.



Further study may narrow the gap. The inferior efficacy of transepithelial CXL may be attributed to factors such as insufficient penetration of riboflavin into the

stroma, the authors noted. This suggests a potential for refining the protocol to achieve an approach that is both safe and more effective.

"There certainly needs to be a discussion around this finding and how it might impact protocol selection. The reason we maintain that transepithelial CXL is inferior in efficacy to conventional CXL is that it is also associated with increased rates of disease progression," Dr. Nath said. "More rigorous trials may find the two CXL protocols even closer in efficacy than currently reported."

—Miriam Karmel

1 Nath S et al. *Ophthalmology*. Published online Dec. 28, 2020.

Relevant financial disclosures—Dr. Nath: None.

connection in neurodegenerative diseases, said Dilraj S. Grewal, MD, at Duke University School of Medicine in Durham, North Carolina. “As the eye serves as the ‘window to the brain,’ noninvasive retinal imaging techniques can visualize the microvasculature in fine detail, which may help detect early neurodegenerative changes,” he said.

Imaging parameters. For this cross-sectional study, the researchers included 69 individuals with PD (124 eyes) and 137 age- and sex-matched healthy controls (248 eyes). All participants were age 50 or older; individuals were excluded if they had another dementia, glaucoma, diabetes, retinal pathology, or corrected visual acuity worse than 20/40.

All eyes underwent OCTA imaging to characterize superficial capillary plexus vessel density (VD), perfusion density (PFD), and foveal avascular zone (FAZ) area. Other OCT biomarkers included retinal nerve fiber layer (RNFL) thickness, macular ganglion cell-inner plexiform layer (GCIPL) thickness, and central subfield thickness (CST) as well as subfoveal choroidal thickness (SFCT), total choroidal area, and luminal area. A choroidal vascularity index (CVI) was calculated by dividing the luminal area by the total choroidal area.

Group differences and similarities. Retinal microvasculature alterations were seen in individuals with PD; these patients had decreased VD and PFD compared to controls. The PD cohort also had structural alterations in the choroid not observed in controls, with a decreased CVI. But both groups were similar in terms of CST, GCIPL thickness, and RNFL thickness. And neither SFCT nor the FAZ area differed between groups.

Of modest clinical value? The statistical analysis suggests that differences observed between the PD and control groups were only moderately useful as independent disease biomarkers with prescribed cutoff values that define disease presence or absence. Coauthor Sharon Fekrat, MD, said a solution more sophisticated than a simple cutoff

value is needed, such as a diagnostic index incorporating multiple retinal and choroidal imaging parameters or deep learning analysis of images.

Going forward. “The greatest challenge to the broad implementation of this approach is the specificity of these findings,” Dr. Grewal said. After all, he noted, retinal microvascular changes are also seen in diseases such as diabetes, glaucoma, and hypertension, all of which tend to be more common in older adults. “We need to determine how the pattern of retinal changes in PD differs from these comorbidities,” he added. “Now that we know that retinal microvascular density and choroidal area/vascularity index are important parameters in Parkinson, there are multiple areas for future research.”

—Miriam Karmel

1 Robbins CB et al. *JAMA Ophthalmol*. Published online Dec. 23, 2020.

2 Yoon SP et al. *Ophthalmol Retina*. 2019;3(6):489-499.

Relevant financial disclosures—Drs. Fekrat and Grewal: None.

PEDIATRICS

Zika's Impact After Birth

Despite having congenital ocular malformations, infants infected prenatally with the Zika virus (ZIKV) appear to undergo normal eye development after birth, results of a study in primates indicate.¹

Fetal and neonatal birth defects associated with ZIKV include retinal colobomas and other ocular anomalies,

microcephaly, musculoskeletal contractions, and neurological deficits. Some prenatally infected babies are born without microcephaly but with eye defects, noted study coauthor Glenn Chung-Wing Yiu, MD, PhD, at the University of California, Davis.

“Before our study,” Dr. Yiu said, “it was unclear if the virus continues to replicate or affect eye development after birth.”

Study specifics. Dr. Yiu and his colleagues infected six pregnant rhesus monkeys with ZIKV during their first trimester. Early fetal loss or stillbirth occurred in four monkeys, but the other two gave birth to infants whose eye development was monitored for two years.

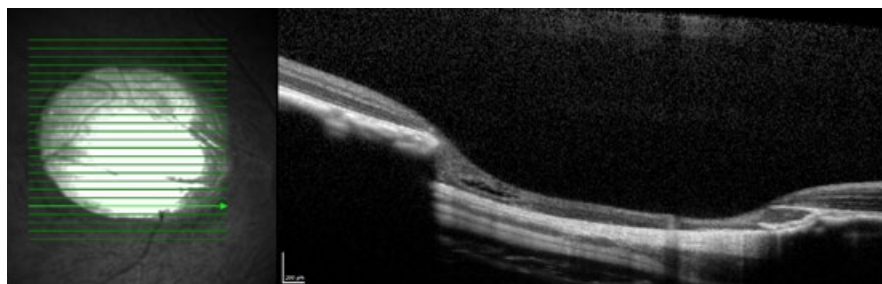
Outcomes. Neither infant had neurological or behavioral defects, and there was no indication of continued viral replication after birth, the researchers found.

Both eyes of one monkey showed large retinal colobomas, as well as thinning of photoreceptor and retinal ganglion cell layers as compared with normal infant monkeys, Dr. Yiu said. Despite the colobomas, the eyes showed normal axial elongation and development of retinal layers as the infant grew, he said.

Pre- versus postnatal. The findings indicate that the ocular impacts of ZIKV infection occur primarily in utero, with no sign of active ZIKV replication after birth, Dr. Yiu said. “This should be reassuring to ophthalmologists following children with this condition.” —Linda Roach

1 Yiu G et al. *JCI Insight*. 2020;5(24):143947.

Relevant financial disclosures—Dr. Yiu: None.



COLOBOMA. Near infrared and optical coherence tomography images of a chorio-retinal coloboma in an infant rhesus monkey that was infected with ZIKV in utero.

See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.