News in Review

COMMENTARY AND PERSPECTIVES

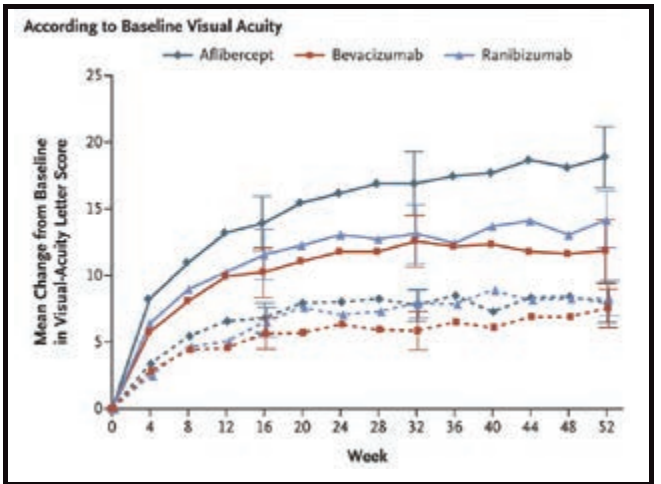
DME Trial Compares 3 Anti-VEGF Drugs

Patients with mild visual loss from diabetic macular edema (DME) benefit similarly, on average, from intravitreous (IVT) injections containing any of three anti-VEGF medications, a head-to-head comparison trial has demonstrated. But in eyes with best-corrected acuity of 20/50 or worse, the visual gains at 12 months were significantly greater with one of the drugs, aflibercept (Eylea).[1]

"This is really the first study that I'm aware of that has shown a difference in therapeutic impact between one anti-VEGF agent and another one in diabetic retinopathy," said study coauthor John A. Wells III, MD, who is in practice at Palmetto Retina Center and chair of ophthalmology at the University of South Carolina, in Columbia.

The results were reported in the *New England Journal of Medicine* by the Diabetic Retinopathy Clinical Research Network (DRCR.net). Since 2003, this nationwide collaborative, funded by the National Eye Institute, has been overseeing landmark studies to identify effective treatments for diabetic eye diseases.

Study details and results. This latest study, Protocol T, was an 89-site, randomized clinical trial comparing the results of IVT therapy with aflibercept, bevacizumab (Avastin), or ranibizumab (Lucentis) in 660 patients with DME. At 12 months, the patients' visual gains were evaluated on a 0 to 100 letter score, with 85 letters approximately 20/20.



VISUAL CHANGE OVER TIME. Solid lines indicate visual acuity (VA) of 20/50 or worse at baseline; dashed lines show baseline VA of 20/32 to 20/40. (I-bars indicate 95 percent confidence intervals.)

In the eyes that were correctable to a letter score of 78 to 69 (approximately 20/32-20/40) at baseline, the mean gain after 12 months was 8.0 letters with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab ($p > .50$ for each pairwise comparison).

But if the initial letter score measured less than 69 (approximately 20/50 or worse), the mean improvement a year later was 18.9 letters with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab ($p < .001$ for aflibercept vs. bevacizumab; $p = .003$ for aflibercept vs. ranibizumab; $p = .21$ for ranibizumab vs. bevacizumab).

Clinical implications. Dr. Wells said that these acuity-specific findings will help clinicians weigh the differences between a

drug that costs about $50 per dose (bevacizumab) and the costlier aflibercept (about $1,950 per dose) or ranibizumab (about $1,200 per dose).

"It's reassuring to know that if the patient has 20/40 or 20/32 vision before treatment, you're going to get about the same level of improvement on average with any of the three drugs, including Avastin," Dr. Wells said. "You can be very comfortable considering using it in this way."

More study needed. Additional papers are planned to look at the results in more detail, Dr. Wells added. "Because one thing that we did see in this study was that the eyes treated with Avastin had significantly less reduction in the macular edema than occurred with the other two drugs," he said. "The long-term impact of this is unknown, but patients are being treated in the study for two years, so we hope to learn more from the second-year results." —*Linda Roach*

1 The Diabetic Retinopathy Clinical Research Network. *N Engl J Med.* 2015 Feb. 18. [Epub ahead of print.]

***Dr. Wells** reports grant support, outside of the work in this study, from Genentech, Regeneron, Allergan, and KalVista.*

Retina Systematic Review

Evidence for Tx in CRVO Macular Edema

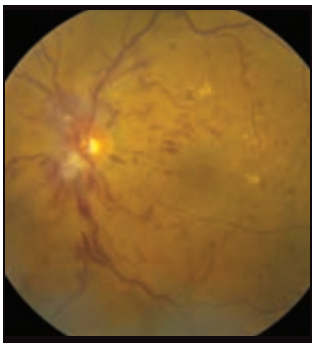
From SCORE and CRUISE to COPERNICUS and GALILEO, numerous studies have shed light on the safety and efficacy of therapies for macular edema (ME) related to central retinal vein occlusion (CRVO). Recently, the Academy's *Ophthalmic Technology Assessment (OTA)* committee reviewed the literature on treatment of ME linked with CRVO and encapsulated high-level evidence for clinicians.[1]

Role of the *OTA*. The *OTA* committee consists of vitreoretinal physicians and a methodologist, who evaluate new and existing therapies and diagnostic tests for retinal disorders, said Steven Yeh, MD, lead author and associate professor of ophthalmology at Emory University in Atlanta.

"One of the main goals is to evaluate the quality of the evidence and to formulate an assessment of various therapies' clinical effectiveness and safety," he said. "This is vetted not only by the *OTA* committee, but also by the American Academy of Ophthalmology and major retinal organizations, including the Macula Society, Retina Society, and American Society of Retina Specialists."

Robust evidence for anti-VEGF. Targeting a condition that affects at least 2.5 million people worldwide, the *OTA* committee searched PubMed and the Cochrane Library and identified 108 citations on CRVO, of which 20 were clinically relevant for review.[1] "We found a high level of level 1 evidence [seven citations representing four clinical trials] supporting the use of anti–vascular endothelial growth factor therapy for ME associated with CRVO," said Dr. Yeh. "All three major anti-VEGF agents—intravitreal [IVT] ranibizumab, aflibercept, and bevacizumab—demonstrated improvements in visual acuity and reduction of macular edema as seen with OCT scanning."

In these trials, early treatment was vital for achieving a three-line visual gain, added Dr. Yeh. "The likelihood of visual gain decreased by almost 50 percent in all three treatment groups if treatment was withheld during the first six months."



CRVO. A recent Academy *OTA* evaluated evidence supporting various therapies for CRVO-related macular edema.

Other therapies. In addition, there was level 1 evidence supporting the efficacy of IVT corticosteroid therapy, either triamcinolone injection (two citations) or dexamethasone implant (one citation). When compared with anti-VEGF therapies, however, steroids were associated with a higher frequency of cataract and glaucoma.

Level 1 evidence from one citation also revealed limited benefits from macular grid laser photocoagulation. Other citations reviewed by the committee demonstrated levels 2 and 3 evidence on that therapy.

Remaining questions. Variations in study designs and protocols sometimes made "apples-to-apples" comparisons difficult, noted Dr. Yeh. For example, patients were excluded from the CRUISE study if they had a relative afferent pupillary defect and ME for more than 12 months, but they were allowed in SCORE.

"Without the benefit of very strict comparative efficacy studies, you can overinterpret or underinterpret differences in efficacy outcomes of treatment groups," he said.

Although this *OTA* review provides strong guidance for clinicians, said Dr. Yeh, additional research is needed in areas such as combination therapies, treatment algorithms, and novel delivery methods.

"There may not be a cookbook recipe for CRVO," he said, "especially given that macular ischemia and inflammation play a stronger role in some of these patients than in others." —*Annie Stuart*

1 Yeh S et al. *Ophthalmology.* 2015;122(4):769-778.

***Dr. Yeh** is a consultant for Clearside Biomedical.*

STEVEN YEH, MD

Regulatory Impacts

Shining a Light on Payments to Eye M.D.s

A retrospective review of data released to the public by the Centers for Medicare & Medicaid Services (CMS), covering Aug. 1 through Dec. 31, 2013, found that most individual payments by industry to ophthalmologists are fairly small, with the largest dollar amounts going to relatively few recipients.[1]

During those five months, drug companies, device makers, and other entities made nearly 56,000 individual payments, totaling almost $11 million, to 9,855 ophthalmologists. These payments covered everything from meals to consulting arrangements, speakers' fees, and royalties.

Payment practices. Some key findings on payments to ophthalmologists are as follows:

- More than 86 percent of individual payments were for food and beverage, though this represented only 15 percent of total spending.
- Nearly three-fourths of payments were $50 or less.
- The greatest percentage of total spending went to consulting fees.
- Payments to ophthalmologists were in line with payments in other subspecialties, including dermatology, orthopedic surgery, urology, and neurosurgery.

What does it mean? The expenditure reports, mandated by the 2010 Physician Payments Sunshine Act, are intended to bring transparency to the relationship between physicians and industry. "It seems difficult to know what the significance is of seeing a physician's name associated with these payments," said Jonathan S. Chang, MD, who reviewed the data. "But studies have shown that industry spending can influence physician decision making despite the fact that physicians themselves do not believe that they are greatly influenced."

Going forward, it would help to see the data in the context of prescribing and practice patterns, which are reported separately by CMS, said Dr. Chang, who is assistant professor of ophthalmology at Columbia University.

For now, he said, "We need to be aware of what is being reported about ourselves and each other because, despite limitations in the data, policymakers will use this information to affect future decision making, practice patterns, and reimbursements."

—Miriam Karmel

1 Chang JS. *Ophthalmology.* 2015;122(4):656-661.

Dr. Chang reports no related financial interests.

Glaucoma Risk Factors

Mitral Valve Prolapse Linked With Glaucoma

In the first published report on the relationship between mitral valve prolapse (MVP) and open-angle glaucoma (OAG), researchers showed that preexisting MVP is a significant predictor for the development of OAG.[1]

MVP and OAG exhibit a similar pathophysiology in the mitral valve and the extracellular matrix of the trabecular meshwork: the excessive accumulation of collagen. This can cause myxomatous degeneration of the valve leaflets in the heart; in the eye, it may affect aqueous outflow facility. Thus, author Shuo-Ju Chiang, MD, PhD, a cardiologist at Taipei Medical University, hypothesized that people with MVP would have a higher incidence of OAG.

Sifting through a large database. He and his colleagues searched for correlations in Taiwan's Longitudinal Health Insurance Database, following 21,677 patients with MVP for 12 years. A comparison group of 86,708 individuals was randomly selected to increase the statistical power. "Our case number was large enough to prove our hypothesis," said Dr. Chiang.

After adjusting for confounding factors, the researchers found an overall hazard ratio of 1.88 (95 percent CI, 1.58-2.23) for OAG in the MVP group compared with controls.

Study limitations. One potential weakness of the study was the high number of confounding variables, as many conditions may affect OAG. To reduce confounding, the two groups were matched for factors including age, sex, heart disease, cerebrovascular disease, coronary artery disease, hyperlipidemia, hypertension, diabetes, migraine, sleep apnea, and myopia.

However, there were no data on other possible risk factors, such as smoking, race, and body mass index. Further, because MVP is often asymptomatic, it might have been underdiagnosed, masking the true association between MVP and OAG.

Recommendations. Dr. Chiang noted that further studies are needed to confirm these findings and to clarify the underlying mechanism. Meanwhile, he recommended: "The measurement of ocular pressure is needed earlier and more frequently in patients with MVP to achieve early diagnosis and treatment of OAG." *—Gabrielle Weiner*

1 Chiang SJ et al. *Heart.* 2014; 101(8):609-615.

Dr. Chiang reports no related financial interests.