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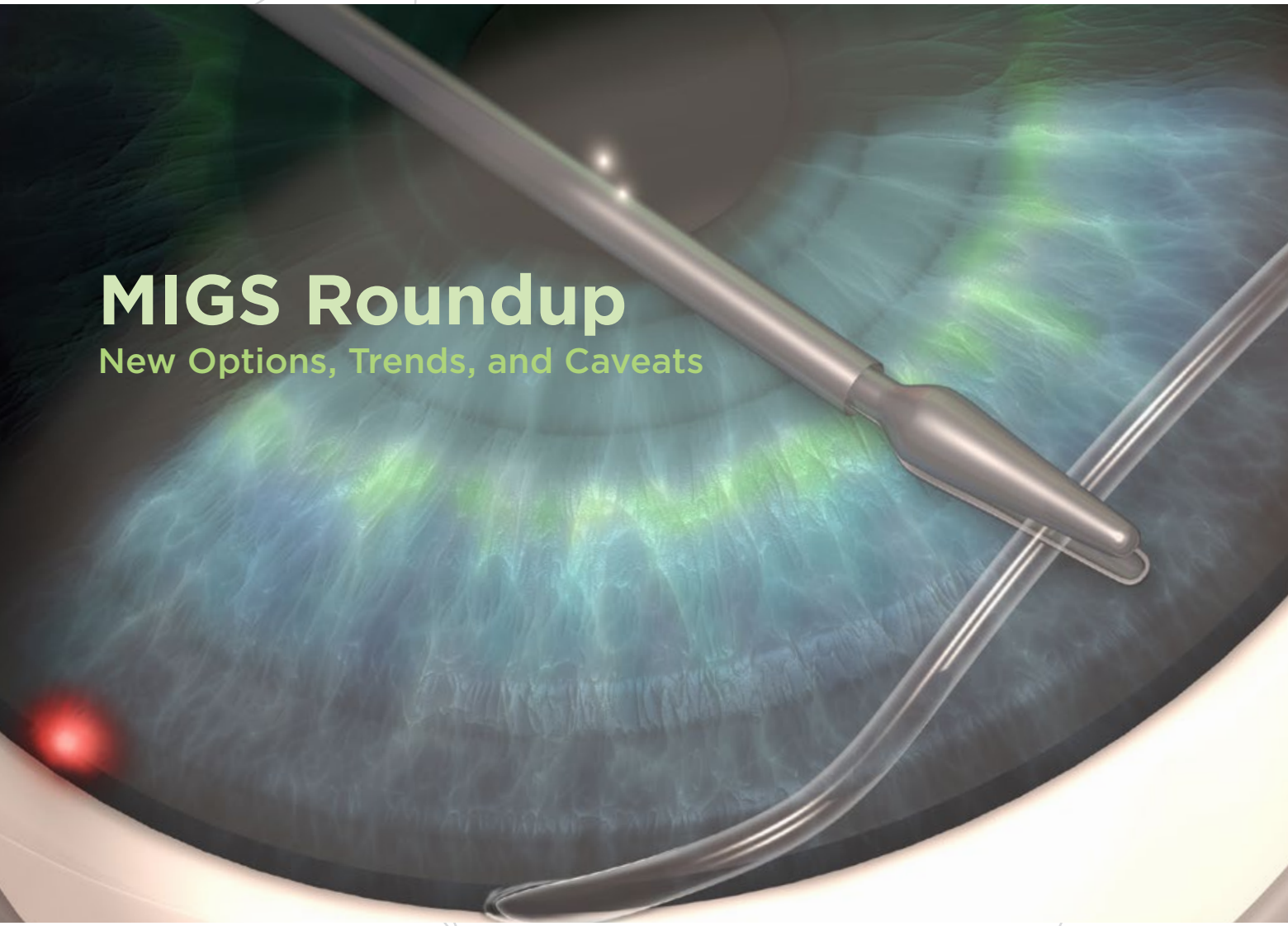

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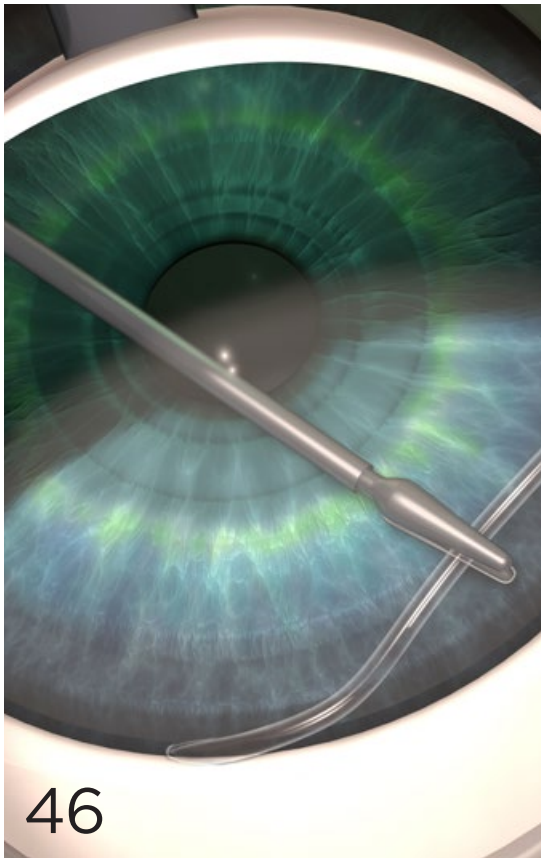

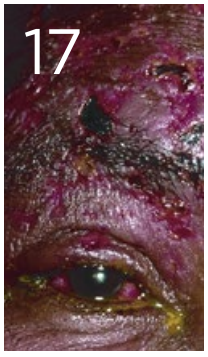

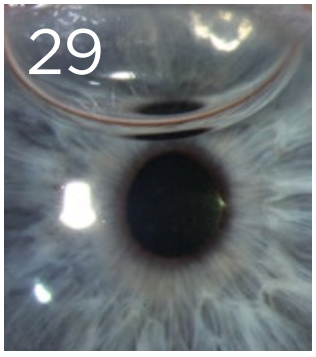

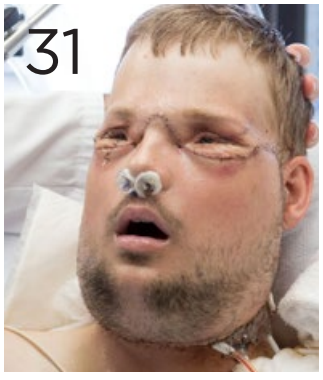

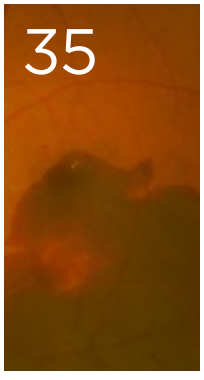

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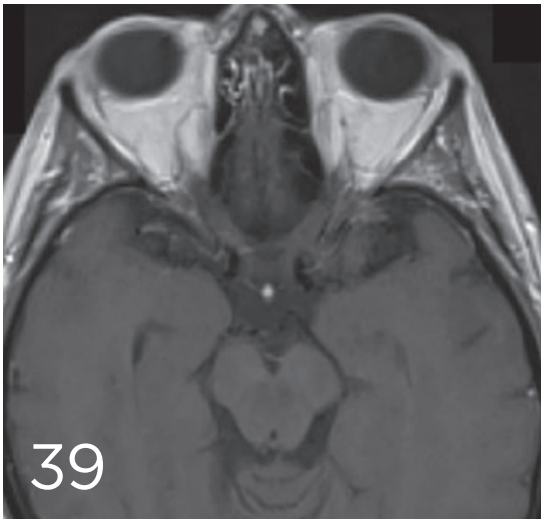

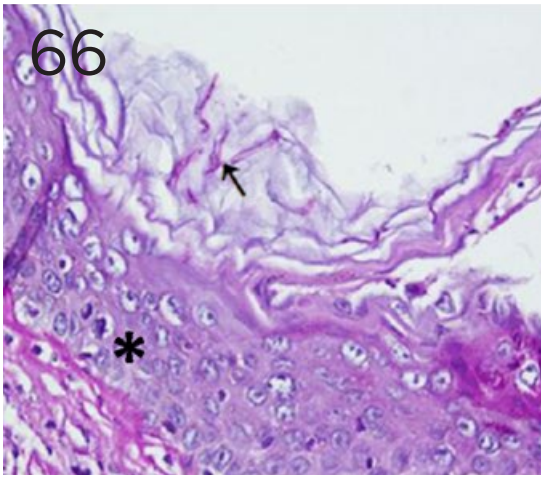

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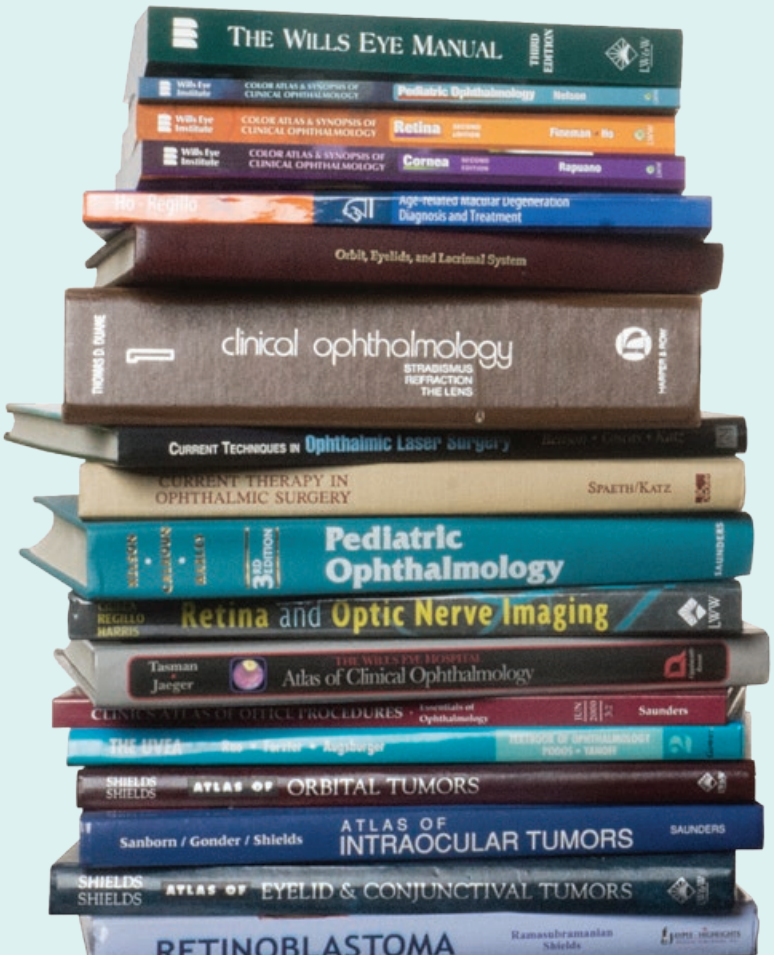

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Letters

Bioptic Telescopic Lenses: Safety Statistics

The article on bioptic telescopic lenses (Clinical Update, October) did not list important safety statistics. Many states do not have safety data available or have not done recent surveys, but some data are available. A summary of bioptic driving safety statistics was published by Dougherty in 2015.[1] The data in his tables and references indicate that the motor vehicle crash rate for bioptic lens wearers in California was 1.9 times higher than that of the control population. The crash rate for bioptic drivers in New York was 1.3 times the normal rate. The crash rate in Ohio was 3 to 4 times the normal.[2] Maine discontinued bioptic driver's licenses in 1983 after there were 10 crashes with 4 fatalities among the state's 22 bioptic lens drivers between 1976 and 1983.[3]

It is likely that this crash rate difference is even greater if the data are converted into crashes per million miles driven. Although data collection is different in different states, there is no doubt that the motor vehicle crash rate for bioptic lens drivers is high; i.e., not safe. Whether that is due to distraction caused by the device, peripheral scotomas, or a combination of factors is open for debate. There is ample evidence for increased crashes while wearing bioptic lenses, but the data show little evidence of increased crash rates from driving with decreased visual acuity; therefore, Maine has relaxed its visual acuity standards for getting a driver's license and will monitor the crash rates following this change to be sure that the new visual acuity standards are safe. The state will not permit bioptic lenses for passing the driving test.

Robert J. Dreher, MD, FACS
Rockport, Maine

1 Dougherty BE et al. *Invest Ophthalmol Vis Sci.* 2015;56(11):6326-6332.
2 Dougherty BE et al. *Invest Ophthalmol Vis Sci.* 2014;55(4):4135.
3 Bioptic Lens Drivers 1976-1982 (Maine Bureau of Motor Vehicles 2/18/83); Duane Brunell, Maine Department of Transportation.

RESPONSE FROM THE EDITORS

The 2015 article that Dr. Dreher cites found that the crash rate was high among bioptic drivers who had no previous driving experience but much lower among those with previous nonbioptic driving experience. In addition, the crash rate of the new drivers decreased as they gained experience. Dr. Dreher accurately reflects what the research found. What is missing is if the drivers had training, and, if so, how much and what type—and if they passed road tests before licensing. In Michigan, for instance, bioptic candidates must go through extensive off- and onroad training and pass 2 tests, and they are restricted to daytime and a small area until they have demonstrated after a year that they can drive safely.

In my opinion, statements about bioptic driving being dangerous should be sure to include information about the circumstances of licensing available.

Lylas G. Mogk, MD
EyeNet Editorial Board, Low Vision Section

The Who, What, When, and Why of Mid-Year Forum 2018, April 18-21

There has been a lot of activity in Washington since last year's Mid-Year Forum, and several battles continue. In particular, we must strive to prevent physicians from being penalized for receiving Part B drug payments—implementation of this damaging policy could cost you upward of $100,000 in annual penalties. When it comes to advocating for your patients and profession, there is no better meeting than the Academy's Mid-Year Forum in Washington, D.C.

Who. At the Mid-Year Forum 2017, several hundred ophthalmologists, including more than 170 residents and fellows, came to Capitol Hill and advocated for ophthalmology. Our team from Florida met with 6 representatives to discuss issues. We expect an even better turnout in 2018.

What and when. The forum begins with a dinner briefing on April 18 to prepare you for the next day's meetings with senators and representatives. On the 19th, during the Congressional Advocacy Day, you will visit Capitol Hill to meet with members of Congress and their staff and discuss the most pressing issues affecting our profession. That evening, a welcome reception begins at 6:00 p.m., followed by a dinner featuring keynote speaker and astronaut David Wolf, MD, EE. The Mid-Year Forum continues the next day and will cover a variety of salient issues, including drug access, pricing, and payment in 2018, as well as the future of artificial intelligence in ophthalmology. The forum will also provide programming for members in training via the Advocacy Ambassador Program, including the L.E.A.P. Forward (Leadership, Engagement, Advocacy, Practice Management) session. Finally, the Academy Council's spring meeting takes place April 20-21, during which the council and leaders of state, subspecialty, and specialized interest societies discuss advocacy news and provide updates on activities and strategic issues.

Why. When you explain to senators and representatives how their votes impact their constituents, you vividly reinforce the advocacy work that the Academy conducts throughout the year. Your personal interactions with your representatives will change the course of ophthalmology. Register by March 6 to receive a discounted rate at aao.org/myf.

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Opinion

RUTH D. WILLIAMS, MD

Why Consensus Statements Matter

Margaret Thatcher didn't value consensus much. While giving a lecture in 1981, the Iron Lady proclaimed, "To me, consensus seems to be the process of abandoning all beliefs, principles, values, and policies. So it is something in which no one believes and to which no one objects."

Consensus, however, has merit in medicine. Consensus statements are often developed to provide guidance when information is evolving and standards of care are not clear. They are described as "a snapshot in time,"[1] as they are developed during a period of change marked by gaps in information.

How are the statements created? Typically, a panel of experts convenes to review the evidence base, identify research gaps, and make recommendations. The resulting statement is an authoritative community-based document that synthesizes emerging information for physicians.

For ophthalmology, recent statements in 2 subspecialties caught my eye. In both areas, new information and new technology introduced variations in care—and, in both, a consensus panel provided guidelines.

Alison Skalet, an ocular oncologist in Portland, Oregon, observed that no guidelines existed for screening children with a family history of retinoblastoma. "We were concerned that this might lead to late diagnosis in some children, while others with very low risk were perhaps undergoing overly aggressive screening. In addition, genetic testing for retinoblastoma, which helps to stratify risk, wasn't uniformly available in the United States."

Ophthalmology published the statement that grew out of conversations about genetic testing and screening protocols for children with a risk of retinoblastoma.[2] The corresponding author of the paper, Patricia Chévez-Barrios, an ophthalmic pathologist in Houston, described the intensive 2-year process of developing the guidelines. "Alison discussed the possibility of a consensus statement with her colleagues Dan Gombos and Jonathan Kim, and with my help developed a panel with a representative from each of the major North American retinoblastoma centers." The process included emails, conference calls, and face-to-face meetings. Later, the Academy and several other medical societies were invited to endorse the statement and suggest any needed changes to the final manuscript. Dan, an ocular oncologist who also practices in Houston, described the resulting consensus statement as a "highly collaborative effort among experts from across the United States and Canada."

On the cataract front, a few years ago, the FDA requested broad input on IOL performance and defining outcomes. Samuel Masket, a cataract surgeon in Los Angeles, described the role of the consensus panel. "Because of innovation in IOL technology, especially in premium IOLs, the FDA needed updated safety and performance endpoints, so the Academy formed a task force of experts to review the existing literature, define gaps in the literature, and make recommendations." The work was published last year in a series of reports in *Ophthalmology*.[3]

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Sam is most intrigued by the current project—involving the Academy, the FDA, the Rand Corporation-UCLA, and members of the ophthalmic IOL manufacturing community—to develop an instrument that evaluates Patient Reported Outcomes (PROs) of premium lenses. This is truly collaborative work that emphasizes outcomes from the perspective of the patient.

It should be noted that consensus statements are not algorithms for care. In ophthalmology, they do not carry the weight of a *Preferred Practice Pattern*. Even so, they can help forge some clarity during times of change. Perhaps one of the most important functions of a consensus work group is to facilitate a discussion, not just with the experts, but with the entire ophthalmic community.

With the increased rate of change in medical knowledge, the role of consensus statements will grow. Even Margaret Thatcher might have agreed.

1 De Boeck K et al. *J Cyst Fibrosis.* 2014:13(5):495-498.

2 Skalet AH et al. *Ophthalmology.* Published online Oct. 18, 2017.

3 See the January 2017 issue of *Ophthalmology*, pp. 133-146.

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1. Yasuda S, Kachi S, Ueno S, Piao CH, Terasaki H. Flicker electroretinograms before and after intravitreal ranibizumab injection in eyes with central retinal vein occlusion. Acta Ophthalmol. 2015;93:e465-8. 2. Moschos MM, Gouliopoulos NS, Kalogeropoulos C. Electrophysiological examination in uveitis: a review of the literature. Clin Ophthalmol. 2014;8:199-214. 3. Larsson J, Andréasson S. Photopic 30 Hz flicker ERG as a predictor for Rubeosis in central retinal vein occlusion. Br J Ophthalmol. 2001;85:683-5. 4. Ratanapakorn T, Patarakittam T, Sinawat S, Sanguansak T, Bhoomibunchoo C, Kaewpanna S, Yospaiboon Y. Effect of cataract on electroretinographic response. J Med Assoc Thai. 2010 Oct;93(10):1196-9. 5. Holm K, Schroeder M, Lövestam Adrian M. Peripheral retinal function assessed with 30-Hz flicker seems to improve after treatment with Lucentis in patients with diabetic macular oedema. Doc Ophthalmol. 2015;131:43-51.

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Current Perspective

DAVID W. PARKE II, MD

Intelligence: Artificial and/or Human

Artificial intelligence (AI) has been widely predicted to change physician work by employing predictive analytics and powering tools that support clinical decision making.

Imagine a 35-year-old Asian woman with Harada's disease on an anti-inflammatory biologic medication with a visually significant cataract. What outcomes can be anticipated with cataract surgery? Traditionally, most ophthalmologists would either call a knowledgeable colleague or search for a recent article on the subject. We would then likely receive either an "expert anecdote" or a small case series that is several years old. By contrast, the combination of clinical decision–support tools, married to a clinical data registry and predictive analytics, might—in a matter of a few minutes—tell you that "of the last 200 Asian women under age 40 on biologics who underwent cataract surgery, X% achieved a visual acuity at 6 months of 20/50 or better and involved treatment with drug Y." Such current and exquisitely specific information could rapidly become invaluable. We've all suffered from cognitive overload. Now we have "artificial" help.

But what of AI's disruptive impact on current models of practice? Most shoes used to be purchased at shoe stores. Now, an increasing percentage are ordered online, and they can be returned for a different size, style, and color. Will glasses become like shoes? And why shouldn't they? But what will be the impact on the ophthalmologist or the optometrist—not just in lost revenue but in dealing with the problems inherent in the process?

How will the diabetic care process be impacted by a technology and analytics platform wherein computer-based image analysis of a single fundus image taken in a pharmacy immediately provides not only retinopathy status but also glycosylated hemoglobin level and cardiovascular risk assessment? That technology exists.

How would the model of macular degeneration (AMD) care be affected by home OCTs (another technology under development)? Does this mean that AMD care only requires an injector? What does it mean for the ophthalmologist? Does patient empowerment necessarily precipitate physician disempowerment? I don't think so, but I do think that technology will fuel greater patient engagement. Consider patient-initiated whole genome sequencing. Based on recent trends, this will soon cost only a few hundred dollars. Examined in isolation, it has limited utility. However, its relevance for patients multiplies when combined with individual clinical and phenotypic information from the electronic health record—and with population-based data from registries!

An analogy has been made to cruise control. We've gone from cruise control to adaptive cruise control to automatic braking for collision avoidance to driverless cars. Advanced imaging and analytics have made this possible. Does this mean that physicians, like drivers, will have far reduced roles and authority? I doubt it. Consider radiology. Its professional demise has been widely predicted for years as images are interpreted by computer. In fact, health care is complicated. Radiologists are assisted by the data processors, not replaced by them. Their workflow has changed. AI can generate probabilities and suggest diagnoses. But AI cannot replace the relationships that physicians develop with patients —which allow us to guide them through the personal risk-benefit trade-offs that characterize clinical disease management. The importance of human intelligence cannot be dismissed.

David W. Parke II, MD
Academy CEO

The ophthalmologist of tomorrow will integrate not only diagnostic information obtained in the office but also information gleaned from wearables and home devices, patient-initiated imaging and genomics, registry-assisted population health information integrated into predictive analytics, and finally the clinical information from face-to-face patient encounters. Our role will evolve; our skill set will evolve; but we will not be supplanted purely by artificial intelligence and technology. AI, by incorporating new datasets, and enriching the analytics, will make physicians more necessary—not less.

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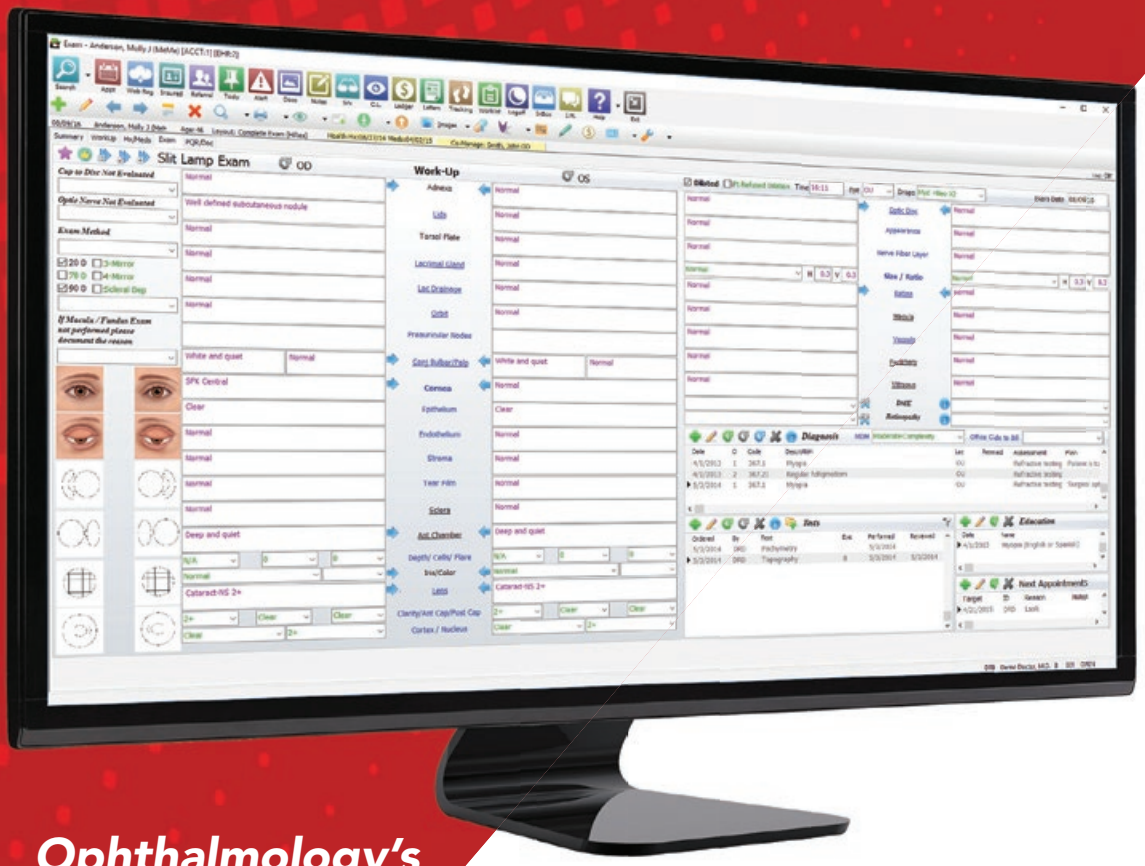

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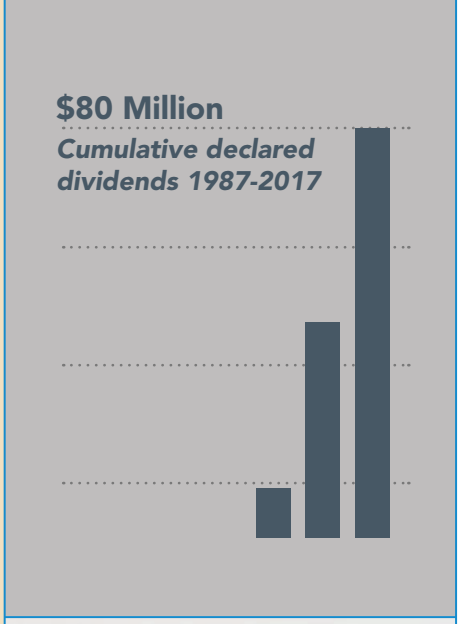

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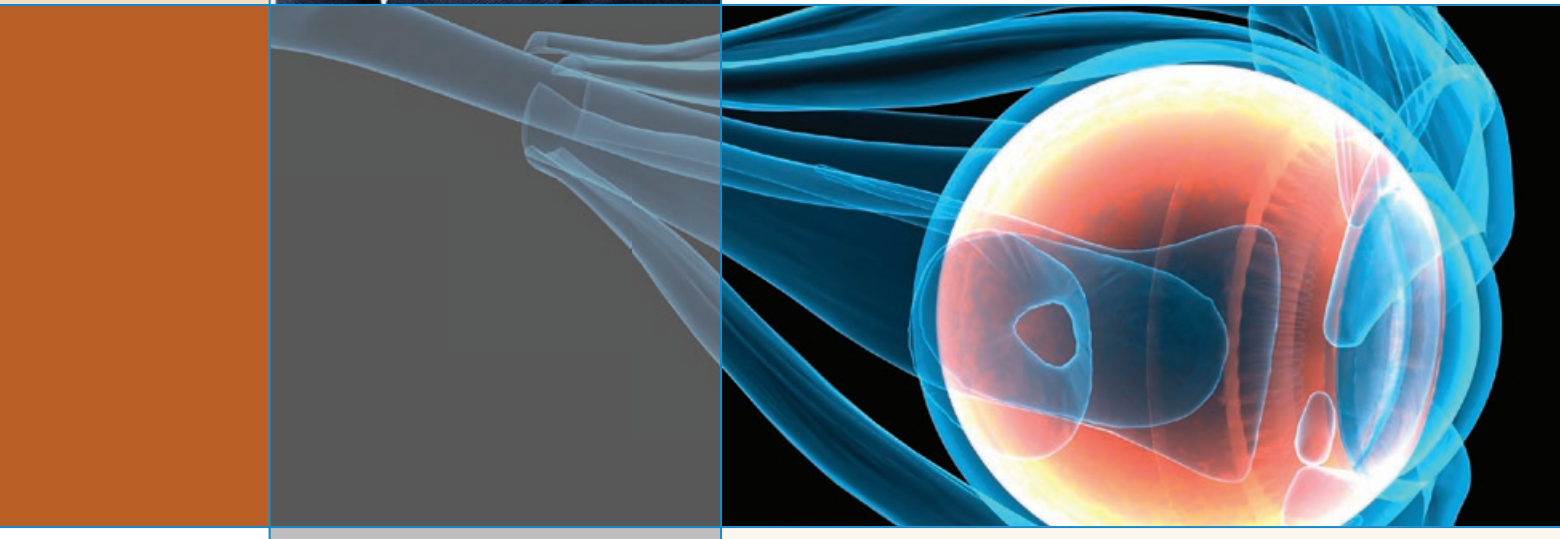

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News in Review

COMMENTARY AND PERSPECTIVE

PUBLIC HEALTH

New Shingles Vaccine Approved

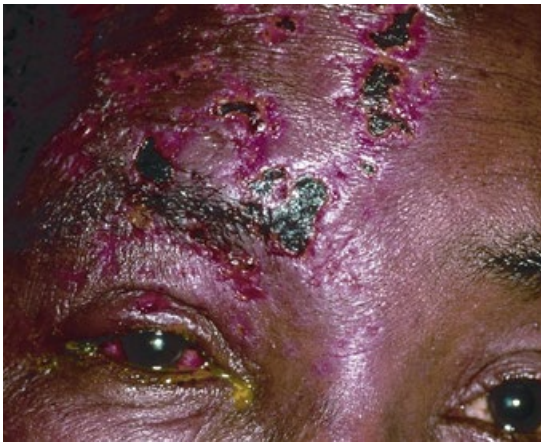
ANYONE WHO HAS HAD SHINGLES knows how painful the condition can be, wherever it occurs on the body. And when the disease manifests as herpes zoster ophthalmicus (HZO), it causes a special, and potentially unending, misery.

But the recent approval of a second vaccine against herpes zoster is offering ophthalmologists a golden opportunity to help patients protect their eyes from HZO. It is recommended that the new vaccine (Shingrix, GlaxoSmithKline), as well as its predecessor (Zostavax, Merck), be given to immunocompetent patients as young as age 50—a decade sooner than earlier recommendations from federal health officials.

Urgent need for immunization. Although the relative merits of the 2 vaccines can be debated, "The real problem is that people are just not getting immunized at all. The penetration is incredibly poor," said cornea specialist Kathryn Colby, MD, PhD, at the University of Chicago. In 2015, only 30.4% of eligible people 60 years and older were vaccinated for zoster.[1]

"Primary care providers don't seem to understand the need to vaccinate against herpes zoster, so it's good for ophthalmologists to educate patients on the benefit—because we're the ones who will end up managing the complications. We need to get the word out, period," said Dr. Colby.

Another cornea specialist, Francis W. Price Jr., MD, said he urges fellow ophthalmologists to advise their patients to protect their vision by getting vaccinated. "I tell my patients that getting shingles in your eye is one of the worst things that can happen to an eye," said Dr. Price, of Price Vision Group in Indianapolis. "Chronic pain from shingles can occur from scarring around the nerve. It can literally go on for the rest of their lives."



PROTECTING VISION. *Approximately 1 in 5 new shingles cases each year is HZO, which can lead to devastating sequelae, including chronic pain, corneal opacification, glaucoma, and retinal disease.*

Recommendations. The FDA approved Shingrix last October with an indication for patients 50 years and older. Shortly afterward, the federal Advisory Committee on Immunization Practices (ACIP) voted to recommend the following:

- Shingrix should be used preferentially over Zostavax, because of clinical trial evidence that the new vaccine is more effective (a > 90% decrease in zoster incidence in all age groups, versus a 70% decrease with Zostavax in people 50-59 years old and 51% in people ≥ 60 years).
- All immunocompetent Americans age 50 and older should be immunized with the new vaccine.
- Patients should receive Shingrix even if previously immunized with Zostavax, as evidence shows that the latter's effectiveness wanes within a few years.

Impact on the eye. Recognition of shingles' potential to cause serious disease, pain, and complications in non-elderly patients has led several medical societies, including the Academy, to recommend that all adults be immunized against herpes zoster beginning at age 50.[2] Some 1.2 million new zoster cases occur each year in the United States; of these, about 20% are HZO.[2]

Complications. Complications of ocular shingles include anterior and posterior segment disease; neurotrophic ocular surface disease; eyelid malpositioning/scarring; and irreversible vision loss due to corneal opacification, glaucoma, and retinal disease.

Dr. Price said that, in his experience, shingles lesions anywhere on the face or head put the patient at risk for HZO. "The textbooks generally say that you get shingles in the eye when you have an outbreak on the tip of your nose. But I've been doing this for over 30 years, and I have seen HZO after lesions located anywhere on the face and head," he said.

What about cost? The Shingrix vaccine requires 2 doses, at least 8 weeks apart, and initially patients may find that insurance coverage of the estimated $280 total cost is spotty. "But I tell

patients that if you've ever known anybody who's had shingles, you'd go out and get vaccinated, whether insurance pays for it or not," Dr. Price said.

—Linda Roach

1 Williams WW et al. *MMWR Surveill Summ.* 2017;66(11):1-28.

2 aao.org/clinical-statement/recommendations-herpes-zoster-vaccine-patients-50-. Accessed Dec. 13, 2017.

Relevant financial disclosures—Drs. Colby and Price: None.

CATARACT

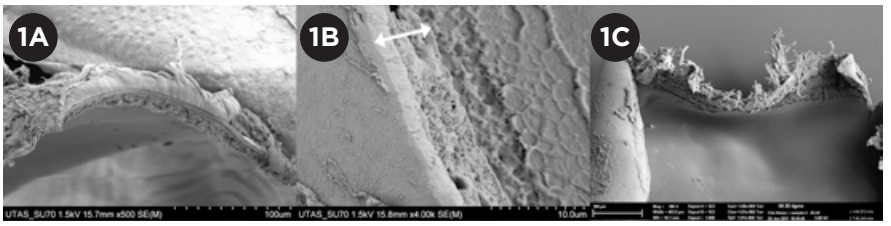
Thermal Device for Capsulotomies Hits Snag

THE POSSIBILITY OF A LOWER-COST alternative to the femtosecond laser for cutting precise, reproducible capsulotomies is attractive, but one such automated device has yielded mixed results, Australian researchers have reported.

The thermal capsulotomy device (Zepto, Mynosys) consists of a disposable handpiece with a circular ring at the tip, attached to a power console. The surgeon inserts the handpiece tip into the anterior chamber through a 2.2-mm incision and places the ring onto the anterior capsule, aligned with the visual axis. The power console then incises the capsule with a ring of 4-millisecond energy pulses.

Study results. In this prospective study, the Zepto successfully created capsulotomies (N = 13) that were central and circular, providing for good intraocular lens position.[1] This was similar to earlier reports by others who conducted preclinical studies and 1 small clinical study.[2]

Irregular margins. However, at the slit lamp, the researchers found that fraying was visible along the thermal capsulotomy margins. Viewed with scanning electron microscopy (SEM), all the capsular buttons had irregularities and frayed collagen fibers along their edges. In contrast, SEM of 2 capsular buttons that were removed after continuous curvilinear capsulorrhexis (CCC) showed they had uniform margins, with no imperfections.



IRREGULARITIES. *Scanning electron microscopy showed areas of irregularity, with different degrees of rolling angle and direction (1A, 1B) and frayed collagen fibers at the capsulotomy margins (1C).*

The propensity for irregular margins on thermal capsulotomies is concerning because this might lead to radial capsular tears, said study coauthor Brendan Vote, MBBS, at the University of Tasmania in Launceston, Australia. "There seemed to be an inherent delivery problem in the device, creating a focal 'hot spot' and weakened capsule in some cases," Dr. Vote said.

Clinical problems. In clinical use in about 125 cases, Dr. Vote said, he and other surgeons in Tasmania and Melbourne also have found that incomplete capsulotomy can be a problem. "We have used the device for about 6 months in total, but we have stopped using it as it was not reliable enough in capsulotomy creation." They also had concerns about potential anterior capsule tears, he said.

Looking ahead. Dr. Vote said he expects the manufacturer to modify the Zepto to address such issues, but an economic roadblock would remain, he said. "Ultimately the biggest barrier to device use, once a satisfactory technical threshold is reached, will be the cost. A per-case cost of $30-$50 would need to be achieved to make incorporating the device into practice cost-effective."

According to the manufacturer, a thermal capsulotomy system sells for about $12,000 in the United States, compared to approximately $500,000 for a femtosecond laser. But each single-use handpiece costs $130 to $165, depending on facility volume.

—Linda Roach

1 Hooshmand J et al. *Ophthalmology.* Published online Oct. 23, 2017.

2 Waltz K et al. *J Cataract Refract Surg.* 2017 May;43(5):606-614.

Relevant financial disclosures—Dr. Vote: None.

NEURO-OPHTHALMOLOGY

Botox Provides Relief for Dry Eye and Photophobia

PATIENTS GIVEN BOTULINUM TOXIN A (Botox) for relief of their migraines might experience a secondary benefit: relief of their symptoms of photophobia and dry eye.[1]

In a retrospective study of patients at the Miami Veteran Affairs Medical Center, researchers from the University of Miami Miller School of Medicine confirmed their hypothesis that migraine, photophobia, and dry eye share neural mechanisms. "We hypothesized that therapies influencing nerve function also influence sensations like dryness and light sensitivity," said Anat Galor, MD, MSPH, "especially the dry-eye subtype we think is more neuropathic."

Relief of symptoms. All 90 patients in the study had chronic migraine (≥ 15 per month) and had failed a trial of at least 2 migraine drugs or had contraindications to these medications.

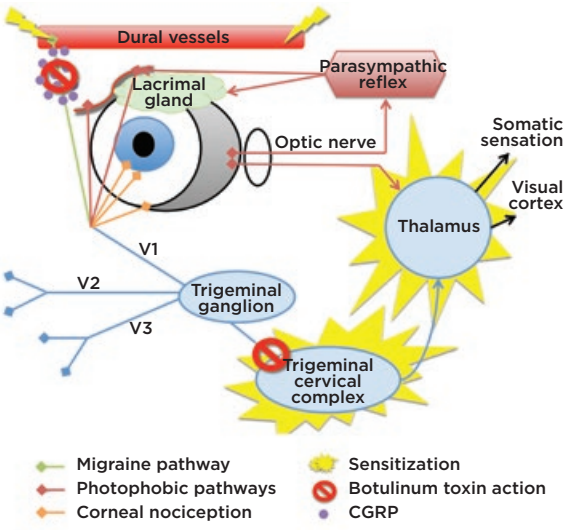
They were asked to recall their ocular symptoms before and after receiving Botox injections and to rate their symptom severity on a scale of 0 to 10. The investigators found that the intensity of all 3 sensations—migraine pain, photophobia, and dryness—was highly correlated, with 72.5% of patients reporting improvement in photophobia and 29.3% reporting improvement in dry eye symptoms. More than a third of patients with photophobia improvement rated it as "much better"; older patients reported more relief in eye pain symptoms.

Inflammatory action. The research-

ers believe that calcitonin gene-related peptide (CGRP) may be central to study results. "One of the proposed mechanisms in migraine is excessive CGRP release, which leads to neurogenic inflammation, recruitment of inflammatory cells to the site, and an inflammatory environment that does further damage to nerves," Dr. Galor said. "You end up with afferent traffic in the trigeminal system that can then sensitize the system."

Up to now, she said, sensations of dryness weren't considered in the same category as migraine pain, "but sensations of dryness and photophobia are also transmitted via trigeminal activation, so sensitization may underlie the correlation among these symptoms."

In the clinic. Ocular pain doesn't always come from the ocular surface, Dr. Galor said. "We have to acknowledge that for a subset of dry-eye patients, the primary problem is nerve sensitization." She added, "This proof-of-concept study suggests that strategies used to treat nerve pain may be effective when clinicians suspect that neuropathic mechanisms underlie dryness and photophobia." *—Rebecca Taylor*



METHOD OF ACTION. *Botulinum toxin A inhibits nociceptive nerve impulses and release of calcitonin gene-related peptide (CGRP) at the trigeminal cervical complex, reducing peripheral and central sensitization and indirectly leading to a reduction in migraine pain, photophobia, and dry eye sensations.*

1 Diel RJ et al. *Ophthalmology*. 2018;125(1):139-140.

Relevant financial disclosures—Dr. Galor: Allergan: C; Shire: C.

RETINA

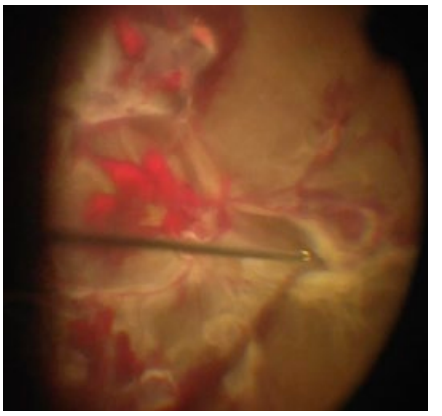
27-Gauge Vitrectomy Surgery: Is Smaller Better?

STUDIES WILL HAVE TO CONFIRM whether the smallest of small-gauge vitrectomy instrumentation is better than earlier generations of fine-gauge instruments. For now, a study shows that the 27-gauge pars plana vitrectomy (PPV) system for posterior segment disease is at least as safe and effective as larger-gauge equivalents.[1]

The retrospective interventional case series involved 360 patients (390 eyes) undergoing 27-gauge PPV (Constellation Vitrectomy 27+ Total Plus Pak, Alcon). "Surgical outcomes were comparable to the initial experience with 23- and 25-gauge instruments, and no new safety concerns were identified at follow-up of at least 1 year," said M. Ali Khan, MD, at the Doheny and Stein Eye Institutes in Los Angeles.

Dr. Khan stressed the importance of a study like this for yielding "real-world outcomes." Surgeons decided which of some 5,000 vitrectomy cases presenting during the study period would undergo 27-gauge PPV. The most common indication was epiretinal membrane (n = 121), followed by vitreous floaters (n = 69) and diabetic tractional retinal detachment (n = 49).

The findings. Across all indications, mean visual acuity improved from 20/105 to 20/50. Postoperative complication rates were low, the most common being transient ocular hypertension (n = 44). Other complications included vitreous hemorrhage, transient hypotony, and cystoid macular edema. Overall, 21% of eyes underwent at least 1 additional intraocular surgery during follow-up, most commonly for cataract extraction.



IN ACTION. *The 27-gauge device in use during repair of a tractional retinal detachment.*

Questions remain. It's still unknown whether a significant difference exists among outcomes using the various small-gauge instruments, but some cases might lend themselves to particular instrumentation, Dr. Khan said. "The 27-gauge system may be preferred in cases with extensive membrane dissection, such as diabetic tractional retinal detachment, during secondary intraocular lens placement, or in situations when biopsy is needed." He added, "In cases when silicone oil is needed or the vitreous/media to be removed is dense, as in a chronic vitreous hemorrhage, a larger-gauge system may be preferred for the increase in flow rate."

An Alcon-sponsored study comparing outcomes in cases randomized to 23-gauge or 27-gauge instrumentation, now in the data analysis phase, may provide more definitive answers.

In the meantime, said Dr. Khan, "I think each of the 27-, 25-, and 23-gauge systems can be used effectively for the surgical management of retinal disease." *—Miriam Karmel*

1 Khan MA et al. *Ophthalmology*. Published online Nov. 13, 2017.

Relevant financial disclosures—Dr. Khan: Allergan: C.

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

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Adjuvant Sunitinib for High-Risk Uveal Melanoma

February 2018

Primary uveal melanoma is the most common primary intraocular malignancy in adults, and effective adjuvant treatment is lacking. Despite definitive treatment of the primary tumor, systemic metastases occur in up to 50% of patients. **Valsecchi et al.** performed a retrospective study of patients with high-risk primary uveal melanoma to compare survival rates between those who received adjuvant sunitinib and those who did not (institutional historical controls). The adjuvant treatment produced promising results that warrant investigation in prospective studies.

For their study, the authors utilized records from the uveal melanoma cytogenetic database of the Wills Eye Hospital Oncology Service.

Outcomes for adults who received adjuvant sunitinib for 6 months (n = 54; median age, 56 years) were compared with outcomes for historical controls in the same risk category (n = 74; median age, 62 years). Kaplan-Meier and Cox proportional hazards models were used to assess overall survival, and propensity scores were used to adjust for nonrandom assignment to sunitinib therapy.

Patients in the sunitinib group exhibited worse cytogenetic or molecular features, had smaller tumors, and were younger. There were 51 deaths: 14 (26%) in the sunitinib group and 37 (50%) among controls. According to univariate analysis, patients treated with sunitinib had longer survival (hazard ratio, 0.53; p = .041). Multivariate Cox regression analysis showed a significant relationship between sunitinib use and age as a dichotomous variable (p = .003).

Factors that were significant in predicting overall survival were cytogenetic/molecular status (p = .015), T-size category (p = .022), gender (p = .040), and adjuvant sunitinib in patients under 60 years of age (p = .004). These findings were confirmed by propensity score analysis.

Although adjuvant sunitinib was associated with longer survival in this study, the findings are limited by the retrospective nature of the research. As a follow-up to this work, the authors are conducting a randomized noncomparative trial of sunitinib and valproic acid. Data obtained from that trial will dictate whether a placebo-controlled study of adjuvant sunitinib should be considered.

Challenges of Type I Boston Keratoprosthesis in Children

February 2018

The Boston type 1 keratoprosthesis (KPro) has become a viable alternative to traditional penetrating keratoplasty (PKP) to treat severe corneal pathology in adults, but little data exist on its use in children.

In a multicenter study, **Fung et al.** documented outcomes and complications of Boston type 1 KPro implantation in children and noted that the procedure is associated with multiple challenges and poor outcomes.

Their study involved reviewing records of patients younger than 17 years of age who underwent KPro surgery at 1 of 3 ophthalmology centers in Canada between January 2010 and November 2014. All procedures were performed by an experienced cornea surgeon. Data were collected and analyzed, including preoperative characteristics, intraoperative complications, postoperative complications, device retention, and best-corrected visual acuity (BCVA).

Before surgery, BCVA ranged from 20/600 to light perception. All of the patients had been diagnosed as having glaucoma, and glaucoma drainage devices (GDDs) had been inserted in 6 eyes before KPro implantation.

The KPro device was implanted in 11 patients (11 eyes) and was the primary corneal procedure in 6 of them. At the most recent exam (mean follow-up, 41.8 months; range, 6.5-85.0 months), 2 eyes had retained their preoperative

BCVA, and 5 eyes lost light perception. Postoperative complications included retroprosthetic membrane (9 eyes), corneal melt (5 eyes), retinal detachment (5 eyes), infectious keratitis (3 eyes), endophthalmitis (3 eyes), and GDD erosion (2 eyes). The initial KPro device was retained in only 4 eyes (36.4%).

This study shows that KPro surgery in children is a major undertaking that can produce permanent and irreversible changes to ocular anatomic features. The authors do not advocate using it in the pediatric population, and all 3 centers involved in this study have stopped offering KPro surgery for children with corneal opacification.

Because the distance between the lens and cornea is short in children, the procedure routinely requires lensectomy and anterior vitrectomy and may warrant subtotal iridectomy and GDDs. Therefore, KPro implantation could subject children to lifelong follow-up, long-term use of topical antibiotics, and perpetual risk of sight-threatening complications.

Intravitreal Bevacizumab or Laser for ROP: 4-Year Outcomes

February 2018

As the survival rate for infants with very low birth weight has increased, so have concerns about improving long-term outcomes for retinopathy of prematurity (ROP). Laser ablation is still the standard of care for ROP, but anti–vascular endothelial growth factor (VEGF) drugs, including intravitreal bevacizumab, have generated interest. To compare long-term outcomes of ROP treatment, **Lepore et al.** conducted a follow-up study of infants born prematurely with type 1, zone 1 disease who had received bevacizumab or undergone laser photoablation. They found that serious ocular effects were more likely to remain in bevacizumab-treated eyes.

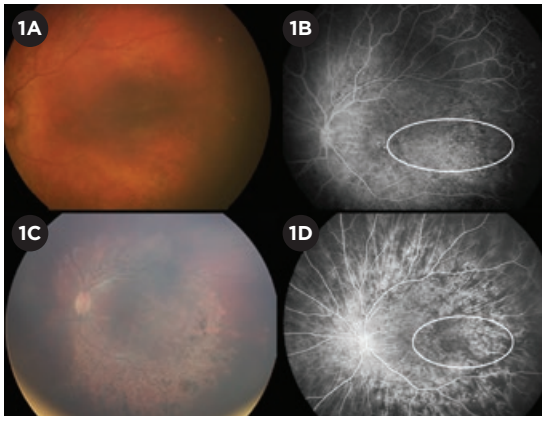
The authors' randomized trial was conducted at Catholic University in Rome from September 2009 through March 2012. Twenty-one infants (42 eyes) received laser photoablation of the peripheral avascular retina in 1 eye and an injection of bevacizumab 0.5 mg in the other. Fluorescein angiography (FA) was performed before and 9 months after treatment. At an average of 4 years after treatment, additional digital retinal and FA images were obtained. Two ROP experts assessed images of 20 eyes in the bevacizumab group and 19 in the laser group for retinal and choroidal features.

At 4 years of age, abnormalities persisted in many bevacizumab-treated eyes, including vessel leakage (13 of 19 eyes), abnormal vessel branching (17 of 20 eyes), vascular tangles (15 of 18 eyes), and shunts (17 of 18 eyes). The authors attributed these problems to ongoing circulation issues. In contrast, fewer laser-treated eyes showed vessel leakage (1 of 18 eyes), abnormal shunts (2 of 19 eyes), or tangles (1 of 18 eyes). No branching abnormalities were observed in this group.

Moreover, at the posterior pole, hyperfluorescent lesions persisted in 55% of bevacizumab-treated eyes and 16% of laser-treated eyes.

The authors noted that many of these outcomes are "worrisome," but they emphasized the importance of FA in identifying unresolved abnormalities. Modalities such as FA and optical coherence tomography could become instrumental in selecting eyes for treatment and determining the timing of interventions. The authors urged clinicians to consider systemic as well as ocular health in their efforts to optimize treatment for infants with serious ROP.

—Summaries by Lynda Seminara



ROP. *Color fundus (1A) and FA (1B) 9 months after bevacizumab injection, with an area of retinal capillary hypoperfusion evident (white circle). Four years later, significant pigmentary abnormalities are evident at the posterior pole (1C), as is a persistent lesion on FA (1D, white circle).*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Serum VEGF Levels and Anti-VEGF Drugs: Results From IVAN

February 2018

Rogers et al. set out to evaluate the potential impact of serum vascular endothelial growth factor (sVEGF) in patients who have neovascular age-related macular degeneration (AMD) and received intravitreal injections of anti-VEGF drugs. In addition, they sought to determine whether there were any associations between sVEGF levels and systemic serious adverse events (SSAEs), notably those of an arteriothrombotic or immunologically mediated nature.

The researchers found that patients who received bevacizumab experienced a greater decrease in sVEGF than did those who received ranibizumab but that this difference was eliminated when treatment ceased for ≥ 3 months. In addition, they found that higher sVEGF levels increased the likelihood that a patient would experience an arteriothrombotic SSAE, while bevacizumab was more likely to raise the risk of an immunologically mediated SSAE.

For this study, the researchers performed an exploratory analysis of data from the IVAN trial, which was conducted in the United Kingdom.

IVAN (Inhibit VEGF in Age-related choroidal Neovascularization) enrolled 610 patients with wet AMD, who were randomized to receive either bevacizumab or ranibizumab. At month 3, after receiving 3 treatments, they were further randomized to either continuous (monthly) dosing or discontinuous treatment (given on an as-needed basis, with those who restarted treatment

mandated to receive 3 consecutive monthly injections). Follow-up extended to 2 years.

Average sVEGF levels were higher in women than in men and in participants who had a history of deep vein thrombosis or pulmonary embolism—and lower in those with a history of myocardial infarction or stroke (including transient ischemic attacks). They did not differ at baseline by age, smoking status, history of heart failure, or diabetes.

On average, sVEGF decreased from a geometric mean of 169 picograms (pg)/mL at baseline to 64 pg/mL at month 24. The decrease was greater in those who received bevacizumab and was apparent by month 1. However, at months 12 and 24, sVEGF levels were similar for the 2 drugs for patients who were 3 months out from treatment.

With regard to SSAEs, 161 of the patients experienced at least 1 SSAE during the trial. Of these, 53 had an arteriothrombotic event and 23 had an immunologically mediated event, and the risk of the latter was higher in those who received bevacizumab. The authors noted that this finding needs to be evaluated in future studies.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Phenotype of Uveitis in Children With Psoriatic Arthritis or Psoriasis

February 2018

Salek et al. pooled the experience of 2 university-based referral centers to begin characterizing the uveitis associated with juvenile psoriatic arthritis and psoriasis. Findings of their study suggest that early-onset juvenile psoriatic arthritis may be a distinct condition, one that is especially severe when it starts before the child is 7 years old.

Study data were collected from Oregon Health & Science University in Portland and the University of Bristol in England. Overall, 6 children were identified (4 boys, 2 girls). Of these, 5 had uveitis and psoriatic arthritis, and 1 had uveitis plus psoriasis. Medical records were reviewed for demographics, descriptions of ocular and joint diseases, medical treatments administered, and complications.

The mean age at presentation was 5.7 years (range, 2-12 years). In 5 of the 6 patients, the disease began before 6 years of age. The uveitis was bilateral in 4 patients. Three patients had anterior uveitis only, and 3 had combined anterior and intermediate uveitis. The response to topical corticosteroids was inadequate in all 6 children. Despite the use of systemic corticosteroids for many months in most of the children, all 6 eventually required methotrexate. Inadequate response to methotrexate resulted in treatment with 1 or more biologic agents in every patient. Five patients underwent at least 1 ophthalmic surgery (e.g., vitrectomy, cataract extraction, glaucoma control).

Although the sample size was small, results indicate that children with psoriasis or psoriatic arthritis occurring by age 6 are at risk for bilateral, chronic, severe uveitis that could warrant biologic therapy as well as surgery.

The differential diagnosis of arthritis associated with psoriasis is extensive. It includes ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, Behçet disease, Kawasaki disease, and sarcoidosis. The authors suggest that early-onset juvenile psoriatic arthritis be added to this list as an entity distinct from other types of psoriatic arthritis.

Scleral Lenses Reduce the Need for Corneal Transplant in Severe Keratoconus

February 2018

Koppen et al. looked at success and failure rates of scleral lens correction for severe keratoconus to determine whether this treatment could be a viable alternative to corneal transplantation. Their research showed that these lenses may spare many patients from the surgery.

The authors' retrospective case series included patients with severe keratoconus (maximal keratometry [Kmax] value ≥ 70 D) who attended the keratoconus clinic at Antwerp University Hospital in Belgium during a 5-year period. Excluded from participation were patients with amblyopia, mental disability, or any concomitant ocular disease that could limit visual potential.

Scleral lens fitting was proposed for 75 eyes; Kmax ranged from 70 to 130 D (mean, 81.70 D). Eight of these eyes underwent corneal transplantation, which was required because of lens intolerance, insufficient visual acuity with the lenses, or problems handling the lenses.

All told, scleral contact lenses were prescribed for 51 of the 75 eyes. The mean gain in visual acuity (scleral lens vs. spectacle-corrected visual acuity) was 0.54 ± 0.18 (decimal fraction, Snellen chart). Seven eyes were lost to follow-up, and lens wear was abandoned in 4 eyes because of the patient's inability to handle the lens. At the most recent follow-up visit, the lens was being worn in 40 eyes (mean follow-up time, 30.15 months).

In summary, 40 (78%) of 51 eyes with severe keratoconus that otherwise would have undergone corneal transplantation were treated successfully with long-term wear of scleral contact lenses.

The authors acknowledge that their keratoconus management strategy, which is focused on specialty contact lenses, may differ from that of other experts. Most importantly, patients should be educated on all treatment options, and the chosen approach should address the unique needs of each person.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Does the Presence of Trainees Have an Effect on the Duration of Patient Appointments?

January 2018

In the current climate of electronic health records (EHR) and value-based reimbursement models, there is constant pressure to improve clinical efficiency. This can be especially challenging for

academic medical centers, where trainees must be educated during the delivery of care. **Goldstein et al.** conducted research at an outpatient ophthalmology clinic and found that the presence of trainees correlated with lengthier appointments.

The single-center cohort study was performed at Oregon Health & Science University in Portland and included 49,448 patient appointments, 33 attending physicians, and 40 trainees. The trainees were residents or clinical fellows in ophthalmology. EHR audit logs were reviewed for time frames of clinical sessions, duration of patient appointments (determined from time stamps), and the presence/absence of a trainee during an appointment or a clinic session. Linear mixed models were devised to address variability among clinicians and patients.

During clinic sessions, patient appointments that involved a trainee were significantly longer than were those without a trainee (mean, 105.0 vs. 80.3 minutes).

Appointments with residents and fellows were 32% and 30% longer, respectively, than appointments without trainees. Presence of a trainee resulted in longer mean appointment times for 29 of the 33 attending physicians, shorter appointment times for 3 physicians, and no change for 1 physician. For all billing levels, trainee presence correlated with longer mean appointment times.

Although the authors acknowledged that study-design limitations can affect data interpretation, their findings highlight the challenge of maintaining efficiency in academic medical centers and raise questions about the suitability of current reimbursement models. The authors hope their work will inspire further research on medical education and clinical workflow, including ways to maximize learning, clinical efficiency, and care quality. They also encourage policy-making discussions of optimal methods to evaluate and reimburse physicians who practice in academic medical centers. *(Also see related commentary by Jennifer L. Lindsey, MD, and Paul Sternberg Jr., MD, in the same issue.)*

Cataract Surgery Reduces Cause-Specific Mortality for Older Women

January 2018

Cataract surgery has been shown to correlate with lower risk of all-cause mortality, potentially because of improved health status and functional independence; however, the association between cataract surgery and cause-specific mortality had not been investigated. To this end, **Tseng et al.** aimed to determine the relationship between cataract surgery and total and cause-specific mortality in older women. Results of their study indicate that this surgery may lower the mortality risk associated with systemic illnesses.

The study included nationwide data of the Women's Health Initiative (WHI), from July 2014 through September 2017, for women ≥ 65 years of age who had cataract. Cataract surgery was determined by Medicare claim codes. Outcomes of interest were all-cause mortality and mortality attributed to cancer, vascular, accidental, neurologic, pulmonary, and infectious causes.

The log-rank test and Cox regression models were used to compare mortality data for patients who did and did not undergo cataract surgery, with adjustments made for demographics, smoking status, alcohol use, body mass index, physical activity, and systemic and ocular comorbidities.

Of the 74,044 women with cataract (mean age, 70.5 years), 41,735 underwent cataract surgery. The crude incidence of all-cause mortality was 1.52 per 100 person-years in the cataract surgery group and 2.56 per 100 person-years in the cataract diagnosis group. Covariate-adjusted Cox models showed a link between cataract surgery and reduced all-cause mortality (adjusted hazards ratio [AHR], 0.40) and between cataract surgery and mortality related to cancer (AHR, 0.31), vascular (AHR, 0.42), accidental (AHR, 0.44), neurologic (AHR, 0.43), pulmonary (AHR, 0.63), and infectious (AHR, 0.44) diseases.

It is unclear whether the favorable associations relate directly to cataract surgery. Patients who underwent the surgery had a much lower mortality rate, despite their overall sicker systemic profile. The authors hypothesize that the mechanism of association is multifactorial and can vary by systemic condition. Whether a patient receives cataract surgery depends on demographic, socioeconomic, and other factors, which warrant exploration. Further study of the relationship between cataract surgery, systemic disease, and disease-related mortality may improve patient care and overall health outcomes. *(Also see related commentary by Justine R. Smith, FRANZCO, PhD, in the same issue.)*

Trial of Dexamethasone Plus Ranibizumab for Persistent DME

January 2018

Although anti–vascular endothelial growth factor (anti-VEGF) therapy is often effective for diabetic macular edema (DME), some patients experience persistent edema and decreased visual acuity despite monthly injection. In a phase 2 randomized clinical trial, **Maturi et al.** added dexamethasone (known to reduce retinal thickening) to ongoing ranibizumab treatment to see if visual outcomes could be improved for patients with persistent DME. After 24 weeks of treatment, visual acuity was no better for patients on combination therapy than for those on ranibizumab alone.

The trial was conducted at 40 U.S. sites between February 2014 and December 2016. Adults who had DME despite ≥ 3 anti-VEGF injections in the previous 20 weeks received 3 additional ranibizumab injections during a 12-week run-in phase. Their visual acuity ranged from 20/32 to 20/320. Eligible patients with persistent DME continued ranibizumab injections and were assigned randomly to receive 700 μg of dexamethasone (combination group) or sham treatment (ranibizumab group). Treatments were administered as often as every 4 weeks, with the schedule based on a structured protocol. The main outcome measure was change in visual acuity letter score from randomization to week 24.

Among the 116 patients (median age, 65 years; 129 eyes), 65 eyes underwent combination treatment and 64 had ranibizumab alone. At 24 weeks, mean (standard deviation [SD]) visual acuity had improved by 2.7 (9.8) letters in the combination group and 3.0 (7.1) letters in the ranibizumab group (adjusted group difference, 0.5 letter; $p = .73$). Mean (SD) change in central subfield thickness was 110 (86) and 62 (97) µm, respectively (adjusted group difference, 52; $p < .001$). Increased intraocular pressure or initiation of antihypertensive eyedrops was reported for 29% of eyes in the combination group and for 0 eyes in the ranibizumab group ($p < .001$).

Despite the significantly greater reduction in retinal thickness in the combination group, adding dexamethasone to ranibizumab treatment did not lead to greater improvement in vision in patients with persistent DME compared to ranibizumab with a sham dexamethasone injection.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Do Hyperreflective Dots on SD-OCT Predict Response to Macular Edema Treatment?

Investigative Ophthalmology & Visual Science
2017;58:5958-5967

Methods to predict therapeutic response may prevent unnecessary treatment and improve outcomes for patients with macular edema. **Hwang et al.** aimed to determine whether the quantity of hyperreflective dots (HRDs) on spectral-domain optical coherence tomography (SD-OCT) at baseline could indicate treatment response to intravitreal bevacizumab or dexamethasone injections in eyes with macular edema. They found that correlations exist but are different for the 2 therapies.

The authors' retrospective study included 82 eyes with diabetic macular edema (DME) and 68 eyes with macular edema from retinal vein occlusion (RVO). Patients with treatment-naïve macular edema initially received 3 consecutive bevacizumab injections, and treatment response was documented. Following these injections, nonresponders received dexamethasone. HRDs were counted manually and independently by 2 masked retina specialists. The authors documented treatment response in relation to best-corrected visual acuity (BCVA), number of HRDs, and incidence of outer plexiform layer (OPL) disruption.

Thirty-six eyes with DME (43.9%) and 22 with RVO (32.4%) did not respond to bevacizumab. The number of baseline HRDs in bevacizumab nonresponders (DME, 16.06 ± 6.60; RVO, 14.23 ± 4.09) was significantly greater than in responders (DME, 11.26 ± 3.64, $p < .001$; RVO, 11.17 ± 4.83, $p = .013$) and did not decline after bevacizumab treatment. Eyes that responded to dexamethasone but not to bevacizumab had significantly more baseline HRDs than eyes that did not respond to either treatment (19.56 ± 6.75 vs. 11.50 ± 3.78; $p = .006$). The OPL disruption rate was significantly higher for bevacizumab nonresponders than responders (DME, $p < .001$; RVO, $p = .001$). BCVA improved in bevacizumab responders but not in bevacizumab nonresponders.

In summary, the number of HRDs on baseline SD-OCT may indicate whether macular edema will improve with intravitreal bevacizumab or dexamethasone. In bevacizumab responders, the number of HRDs was small. The larger number of HRDs in dexamethasone responders may reflect greater inflammation of the retina. Hence, the latter treatment may be most effective in eyes that exhibit many HRDs and OPL disruptions. Large-scale prospective studies that include automated quantification of HRDs are encouraged.

Prospective Trial of Corneal Reconstruction With Biomaterial-Free COMECs

Cornea
2018;37(1):76-83

Conventional therapeutic options for limbal stem cell deficiency (LSCD) are allogenic limbal graft transplantation and autologous conjunctivolimbal graft from the contralateral eye. However, regenerative medicine involving adult stem cells for ocular reconstruction is gaining popularity. **Kim et al.** studied the efficacy and safety of transplanting biomaterial-free cultured oral mucosal epithelial cell sheets (COMECs) for ocular reconstruction in patients with total LSCD. Their findings indicate that the procedure is generally safe and efficacious for this purpose.

For this prospective trial, which was conducted in Seoul, South Korea, the researchers included 8 patients with complete LSCD. COMECs were prepared in a culture system without temperature-sensitive polymers or carriers. The sheets were transplanted but not sutured. After transplant stabilization, 4 patients underwent penetrating keratoplasty. During the subsequent 6 months, the authors documented stability of epithelialization, changes in visual acuity, and postoperative complications. Immunofluorescent staining of corneal cytokeratins (K) was conducted for the patients who underwent penetrating keratoplasty.

The ocular surface was successfully reconstructed in 6 eyes. Complete stable epithelialization was achieved in a mean of 53.6 days. Five eyes had visual improvement of ≥ 2 lines. The procedure failed in 2 eyes, which exhibited full symblepharon in all 4 quadrants. Following keratoplasty, the corneal phenotypic marker (K12) and mucosal phenotypic markers (K4 and K13) were well expressed, suggesting that COMECs acquire part of the corneal phenotype. K1, K8, and K19 showed minimal expression. No ocular infections or noteworthy systemic complications were reported. Finally, local tumor formation was not observed in any patient.

Although these findings indicate that transplantation of biomaterial-free COMECs is generally effective and safe for reconstructing the ocular surface in patients with LSCD, it may be prudent to exclude candidates who have complete symblepharon in all 4 quadrants. Meticulous postoperative care is crucial to maintain stability of the COMECs and to optimize overall outcomes.

—Summaries by Lynda Seminara

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References: 1. *CyPass*® Micro-Stent Instructions for Use. **2.** Vold S, Ahmed IIK, Craven ER, et al. Two-year COMPASS trial results: supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataracts. *Ophthalmology*. 2016;123(10):2103-2112.

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CyPass® Micro-Stent

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CONTRAINDICATIONS: Use of the *CyPass* Micro-Stent is contraindicated in the following circumstances or conditions: (1) in eyes with angle-closure glaucoma; and (2) in eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber angle.

MRI INFORMATION: The *CyPass* Micro-Stent is magnetic resonance (MR) Safe: the implant is constructed of polyimide material, a non-conducting, non-metallic, non-magnetic polymer that poses no known hazards in all magnetic resonance imaging environments.

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ATTENTION: PLEASE REFER TO THE INSTRUCTIONS FOR A COMPLETE LIST OF CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS.

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DMEK Enters the Mainstream

Descemet membrane endothelial keratoplasty (DMEK) appears to be gaining acceptance with cornea surgeons for treatment of patients with corneal endothelial dysfunction.

In DMEK, the endothelium and Descemet membrane (DM) are delivered into the anterior chamber in the form of a scroll that must be unfolded. A number of studies indicate that the procedure offers rapid and predictable visual recovery.[1] And compared with other keratoplasty procedures, it offers a number of benefits, including better quality of vision and a reduced risk of immunologic graft rejection.[1]

Yet cornea surgeons have been slow to adopt the procedure, acknowledged Francis W. Price Jr., MD, of Price Vision Group in Indianapolis. However, he said, "we [now] appear to be at the tipping point where adoption will be more rapid Many training programs are now doing DMEK, and the younger generation of cornea specialists coming out should be trained and familiar" with it.

Gaining Traction

Gerrit R.J. Melles, MD, PhD, agreed that the tide of acceptance has shifted in the last few years, which he attributed to improvements in the surgical procedure and graft preparation techniques.

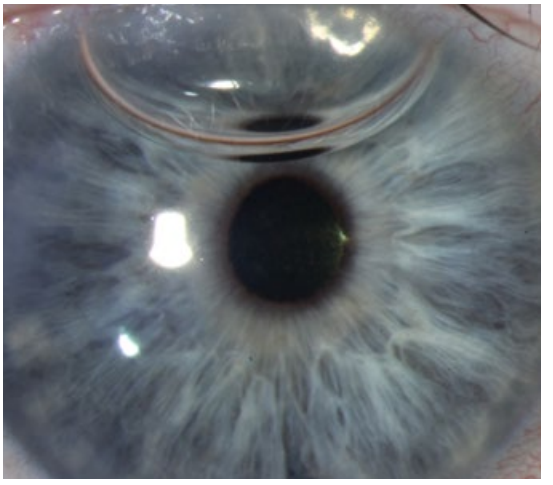
"Given the clinical outcomes and patient satisfaction, DMEK has been gaining traction with ophthalmologists all over the world," said Dr. Melles, of the Netherlands Institute for Innovative Ocular Surgery in Rotterdam. "Currently, DMEK may be feasible for most cornea surgeons in any clinical setting and at a relatively low cost."

Follow the numbers. A recent *Ophthalmic Technology Assessment* (*OTA*) underscores this shift, noting a 64% increase in DMEK procedures from 2014 to 2015.[1] In comparison, the *OTA* found a 4.1% decrease in the number of an earlier EK iteration, DSEK (Descemet stripping EK), since 2013.

And the number of DMEK procedures is doubling every year, according to Mark A. Terry, MD, as the technique continues to be standardized and refined. "I tell surgeons that they should learn to perform DMEK, first focusing on routine cases without other confounding variables," said Dr. Terry, of the Devers Eye Institute in Portland, Oregon.

Bumpy Road to Acceptance

DMEK was first described by Dr. Melles in 2006.[2] As the technique was perfected over the next few years, cornea surgeons reported that they were achieving 20/20 and 20/15 in more than 50% of eyes—and that their patients were experiencing a quicker recovery time.



SIX DAYS OUT. *A DMEK graft 6 days after surgery, the first DMEK procedure to be performed by a cornea fellow. At this point, the patient's vision was 20/30 without correction.*

Game changer. In 2012, Dr. Price and his colleagues found that patients undergoing DMEK were significantly less likely to experience a rejection episode within 2 years after surgery compared with DSEK and PK for similar indications using the same corticosteroid regimen.[3]

These results prompted Dr. Price to revisit his corticosteroid dosing regimen. In a prospective study, he compared intraocular pressure (IOP) elevation and graft rejection with loteprednol etabonate 0.5% gel and prednisolone acetate 1% solution after DMEK. The 2 medications proved equally effective in preventing immunologic rejection episodes (none occurred), and IOP elevation was twice as likely in the prednisolone-treated eyes.[4]

BY LORI BAKER-SCHENA, MBA, EDD, CONTRIBUTING WRITER, INTERVIEWING **GERRIT R.J. MELLES, MD, PHD, FRANCIS W. PRICE JR., MD,** AND **MARK A. TERRY, MD.**

Mark A. Terry, MD

"This was a game changer for us, allowing for a decreased dosage of topical steroid," Dr. Price said.

Key challenges. Despite these and other favorable study results, barriers to DMEK acceptance remained.

Tissue prep. This has been one of the biggest stumbling blocks. "I had been stripping my own DMEK tissue since 2009," Dr. Terry said. "However, surgeons were concerned with the time it took to prepare tissue in the OR, as well as the very real risk of damaging donor tissue."

Dr. Terry and his colleagues overcame this hurdle by working with the local eye bank to provide prestripped donor tissue, which removed the risk for the surgeon without increasing the possibility of graft failure or re-bubbling compared to surgeon-prepared tissue.[5]

Graft orientation. The next barrier for surgeons was to confirm the correct orientation of the DM graft. Dr. Terry worked with the eye bank to perform a novel stromal-sided S-stamp preparation, which safely eliminated upside-down graft implantation.[6]

Graft delivery. "Even with these developments, surgeons were reluctant to adopt DMEK," Dr. Terry said. "They still had to stain, trephinate, and load the graft into an injector, which entailed time and some risk." Once again, he turned to the eye bank, working on the next advance, in which the prestripped, prestamped donor cornea is also preloaded into a glass injector, ready for injection into the patient's eye.[7]

Learning curve. Experienced EK surgeons have been reluctant to adopt the newer technique, given their comfort level and success rate with DSEK (and its automated variation, DSAEK) as well as the technical challenges posed by DMEK. But this is beginning to change, driven by study results and what the *OTA* described as "extensive DMEK educational and skill transfer courses."[1]

What impact does the learning curve have on outcomes? Dr. Melles recently published a multicenter study on approximately 2,500 DMEK eyes performed by different surgeons all over the world, looking at outcomes and complications.[8]

"Technique standardization and surgical experience seem to have a strong effect on the rate of postoperative complications and have especially contributed to fewer graft detachments," he said. "However, experience does not seem to influence postoperative visual acuity outcomes."

Complications. According to the *OTA*, the "types of complications during and after DMEK are similar to those encountered with DSEK."[1] The most common complication has been partial graft detachment; other complications have included graft failure, IOP rise, cystoid macular edema, and endothelial cell loss.[1]

Patient selection. DMEK can be performed concurrently with cataract surgery and in patients with previous trabeculectomy or glaucoma drainage devices.[1]

However, for eyes with large iris defects, aphakia, or significant anterior synechia and scarring, Dr. Price is among those who use DSAEK/DSEK.

What's Next?

Research efforts on deck include the following.

Quarter-DMEK. Dr. Melles and his team are currently evaluating "Quarter-DMEK" for the treatment of Fuchs endothelial dystrophy.[9] This hybrid technique marries DMEK, which provides fast visual recovery, to DM endothelial transfer (DMET), which allows a cornea to clear through donor and/or host endothelial cell migration.

"With Quarter-DMEK, a smaller graft is used to cover the central cornea, to provide fast visual recovery by the presence of donor endothelium within the visual axis, while stimulating host endothelial cells to bridge the area between the edge of the descemetorhexis and the graft itself," Dr. Melles said. (For images, view this article online.)

He noted the added benefit of Quarter-DMEK is that 4 grafts may be prepared from 1 donor eye, which would potentially quadruple the number of transplants from a given donor pool.

Use of glaucoma drugs. Dr. Terry cited projects under study in which the DM is stripped and the eye is treated with the glaucoma medication ripasudil. This stimulates endothelial cells, thus possibly eliminating the need for a corneal transplant altogether.[10] (See the December 2017 *EyeNet* cover story for more about this.)

Dr. Price's center has recently begun a placebo-controlled randomized study to see if one of these glaucoma drugs, a rho-kinase (ROCK) inhibitor, can block the IOP increase seen with topical corticosteroids as well if it has any effect on the donor and recipient cornea.

Evaluation of color perception. Dr. Price's team also has discovered that color discernment usually improves after DMEK in patients with Fuchs,[11] an outcome he hypothesized may be related to the removal of the guttae associated with the condition.

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Dr. Melles is director of the Netherlands Institute for Innovative Ocular Surgery (NIIOS), the Melles Cornea Clinic, and the Amnitrans EyeBank, all in Rotterdam, The Netherlands. He is also director of NIIOS USA, in San Diego. *Relevant financial disclosures: DORC International BV/Dutch Ophthalmic USA: C; SurgiCube International: C.*

Dr. Price practices with Price Vision Group and is the founder of the Cornea Research Foundation of America, both in Indianapolis. *Relevant financial disclosures: None.*

Dr. Terry is director of Cornea Services at Devers Eye Institute and professor of clinical ophthalmology at Oregon Health Science & University, both in Portland. *Relevant financial disclosures: None.*

See the disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.

EXTRA **MORE ONLINE.** For a brief overview of DMEK's history and Quarter-DMEK images, view this article online at aao.org/eyenet.

Facial Transplants: Maximizing Periocular Results

Few procedures rival the intricacies of facial transplants, which have been completed just 38 times around the world, including 13 times in the United States, according to Samir Mardini, MD, at the Mayo Clinic in Rochester, Minnesota. The first—and so far sole—facial transplant at the Mayo Clinic took place in 2016. The procedure took 55 hours and involved more than 100 people, including 9 surgeons, said Elizabeth A. Bradley, MD, also at the Mayo Clinic.

The only way to be successful with such a procedure is to have a well-trained, invested, and collaborative team that's undergone intensive training, said Dr. Mardini. He added that having an oculoplastic surgeon as part of this team is essential for ensuring optimal results. "With a face transplant, there are many issues related to the eyes, including orbital reconstruction, eye protection, and visual acuity."

Patient Selection Is Pivotal

Candidates for facial transplants are most often patients with severe burns, ballistic trauma, animal bites, congenital deformities, or neoplastic conditions.[1] Appropriate patient selection is the No. 1 priority, said Dr. Mardini, and the selection process should include the following.

Evaluation of deformity. Facial transplant candidates have significant functional and aesthetic deficits that are beyond the scope of what other traditional methods can address, said Dr. Bradley. For example, Dr. Mardini said, these individuals often have severe facial deformities that involve facial sphincters such as eyelid or oral sphincters, which are quite challenging to reconstruct successfully with conventional methods.

POSTSURGERY. *Dr. Mardini checks in with the team's first facial transplant recipient, who has since regained his ability to smell, breathe, and eat.*

Thorough screening. It is critical that patients undergo a rigorous, multidisciplinary mental and physical screening, said Dr. Bradley. "For patients, a face transplant is a long haul, and they need to have a supportive care system and understand the enormous commitment involved." The Mayo Clinic has a transplant psychiatrist and social workers who will be integrally involved in screening these patients and guiding them through education, rehabilitation, and postsurgical care, said Dr. Mardini.

Contraindications. "If anyone on the team has a sense that the patient doesn't fully understand the benefits, risks, and implications—including lifelong immunosuppression, major surgery, and rehabilitation—they will not be listed for a face transplant," said Dr. Mardini. Contraindications include being medically unfit or noncompliant, he said. Relative contraindications include different forms of addiction, including smoking and alcohol abuse, which could interfere with the surgery or aftercare.

The Mayo Clinic patient "had gained much maturity and showed no signs of residual mental health issues" 10 years after he had attempted suicide with a gun, Dr. Bradley said. "For these reasons, we felt he should be considered a candidate for face transplantation."

What about blindness? Should blind patients be eligible for face transplants? "This has been a subject of debate," said

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **ELIZABETH A. BRADLEY, MD, MICHAEL P. GRANT, MD, PHD,** AND **SAMIR MARDINI, MD.**

Mayo Clinic, Rochester, Minn.

Dr. Bradley. She explained that there have been concerns that early physical signs of rejection such as swelling and skin erythema might be missed, as well as the contention that the blind are less susceptible to others' reactions.

"However, blind patients are perceptive and can sense people's reactions without visual stimuli," she said. As for signs of rejection, said Dr. Mardini, no patient will undergo the process without having a good social support network, which can help with monitoring. Moreover, blind patients may notice warmth or changes in their skin texture, Dr. Bradley added.

Global Periorbital Goals

"Technically, we are able to transfer any structure, including different tissue types such as bone, muscle, and nerves," said Dr. Mardini. But every anatomic defect is unique, so each facial transplant is individualized for the patient, he said. The periorbital aspects of the surgery are also unique depending upon what is missing or dysfunctional.

Function, protection, aesthetics. For the most part, everything in the face requires functional animation, said Dr. Mardini. For example, restoration of facial anatomy is needed for clear speech and vision, mastication of food, and air humidification.[1]

"With face transplants, you're either transplanting everything or transplanting a part, but the part that is native to the patient needs to be technically well connected to the transplanted part so that it becomes functional," he said.

Goals for periorbital area. "In broad terms, two main goals with composite tissue transplantation in the periorbital area are protecting the eyes and making the periorbital area look as normal as possible," said Michael P. Grant, MD, PhD, at the University of Maryland School of Medicine in Baltimore. "The goal is to replace all damaged layers of tissue—including conjunctiva, skin, and levator tendons—to allow patients to open and close their eyes normally."

Eyelid closure. A full transplant involves all the skin of the face from the forehead down to the neck, said Dr. Bradley, which means the eyelids are transplanted as well. "With full eyelid transplant, the concern is the recovery of the blink because it is so important for corneal health," she said. "These patients may have impaired blink until reinnervation happens, which usually occurs at 6 to 8 months and earlier if the nerves are attached very close to the eyelids."

One factor that may help with eyelid closure in volitional and reflex blink is the replacement of contracted eyelid tissue.[2] The recipient nerves also need to be strong enough to innervate the transplanted eyelids and animate closure, said Dr. Mardini. In reattaching facial nerves, Dr. Grant recommends going out as far as possible on each branch to minimize the time for regeneration. "If you graft the branches as far distal as possible, that cuts your time for reinnervation. That is the single most important thing you can do to help preserve or improve blink."

Impact on vision. Many patients who have severe facial injuries have problems with their vision, said Dr. Grant. "Some have structural problems with their eyes, often from the original injury, resulting in reduced vision. Others have damage to their eyelids or conjunctiva, which results in problems with the ocular surface and exposure that can also diminish vision. Restoring a normal ocular surface can potentially reverse some of these problems and maximize the patient's visual acuity."

Dr. Grant and his colleagues currently have a recipient listed for a face transplant who has serious bilateral scarring in the periorbital region. Multiple previous procedures were unsuccessful at completely closing both eyes, resulting in chronic dry eye and ocular surface disease. "During his facial transplant, we will remove his existing eyelids but preserve as much conjunctiva as possible. From the donor, we'll take both upper and lower eyelids and as much conjunctiva as possible," Dr. Grant said. "Although the patient currently has useful but reduced vision in both eyes, I believe we can significantly improve his vision by restoring the health of the ocular surface."

Preserving sight. In the Mayo Clinic case, the patient had become blind in 1 eye due to ballistic trauma, but he had intact vision in the other eye. "Because we needed to do major orbital reconstructive surgery, my No. 1 goal was to make sure he didn't wake up blind in

Issues With Immunosuppression

Patients who have undergone a facial transplant risk not only rejection but also significant long-term consequences, including cancer, opportunistic infections, metabolic disorders, and death. But "as immunosuppressive strategies improve, I think face transplants will become a more widely accepted solution for severe midfacial injuries involving the periorbital area," said Dr. Grant.

Hospital-acquired infections. On average, face transplant patients undergo anywhere from 1 to 6 revisions, requiring 1- to 3-day hospitalizations, said Dr. Bradley. Patients on immunosuppressants are at greater risk of hospital-acquired infections, so the stakes are much higher, she said.

Risks of rejection. "Currently, we have to be very concerned about rejection, said Dr. Grant. "Skin is very antigenic, and almost all patients have episodes of rejection." These episodes can produce scarring or complete death of the transplanted tissues, including eyelids, added Dr. Mardini. At Mayo Clinic, "our patient had 1 episode of acute rejection that we caught early and treated," he said. It quickly resolved.

Catching rejection early. The Mayo Clinic team had transplanted another part of the donor tissue into the patient's groin area, which created a sentinel flap area for routine biopsies. "From these biopsies, we had picked up that he had a mild form of rejection," said Dr. Mardini. "We then biopsied his face, which correlated with a finding of rejection, and treated him, even though we had not picked up clinically that he had a problem with his face."

the other eye," said Dr. Bradley. "Our repair of his enophthalmos involved the insertion of custom-made implants. During the insertion process, pressure is applied to the orbital soft tissues. If too much pressure is applied, it is possible to cause a severe optic neuropathy with blindness. From a vision standpoint, that is the part of the case I was most concerned about."

Face Transplant Challenges

"What made our surgery complex was transplanting most of the bones of the face with the overlying soft tissues," said Dr. Mardini. "We transplanted the nose and cheeks and all the muscles below the eyelids." The partial transplant, added Dr. Bradley, involved tear drainage systems, the orbital rims, a portion of the floor of the eye socket, and soft tissue dealing with telecanthus —attachments between the eyelids and the nose.

Isolating and connecting nerves. Because the forehead and eyelid skin were preserved, it was necessary to preserve function in those parts, said Dr. Mardini. "The first thing we did was isolate all the facial nerve branches on both sides of the patient, preserving the function of forehead movement and elevation as well as upper and lower eyelid closure. We then used all the other nerve branches below that to provide nerve supply to the transplanted organ."

Dr. Mardini added, "We connected the infraorbital nerves and inferior alveolar nerves to get supply to the cheek, upper and lower lips, and the chin as well as the teeth of the transplant. All the parts of the face that were transplanted became functional, plus the patient maintained the eye closure and forehead movement that he had before the procedure."

Connecting other tissues. The Mayo Clinic patient had his own eyelids, lacrimal gland, and lacrimal drainage system. The tear sac was completely obstructed on one side and partially obstructed on the other. "When we transplanted parts of the nasal bone, maxillary bones, soft tissues of the cheek, chin, and upper and lower jaw, we connected eyelids and the drainage system that he had to the transplanted one," said Dr. Mardini. "This allowed his lacrimal gland to release tears that lubricated the eyelid and moved through the canaliculi to his lacrimal sac, which was connected to the donor lacrimal sac and drained into the transplanted nose."

Addressing unique issues. The Mayo Clinic case posed unique periorbital issues including telecanthus and lack of a nose, which meant there was nothing for the soft tissues to attach to, said Dr. Bradley.

Telecanthus. "To address this, we secured our patient's medial canthal tendon to the donor's robust medial canthal tendon, which was still attached to the donor's nasal bones," said Dr. Bradley. As a result, said Dr. Mardini, today the patient does not have such a wide distance between his medial canthal tendons.

Lacrimal system. Lack of a nose "also meant our patient didn't have an intact lacrimal system on either side," said Dr. Bradley. It's important to remember that a blockage of the lacrimal sac can increase the threat of infection in an immunocompromised patient, she said. "In our case, we were putting in an alloplastic implant, and we knew an infected sac sitting right next to foreign material could pose a threat to the implant."

Swelling. The initial surgery caused massive swelling, said Dr. Bradley, so the surgical team deferred all of the lacrimal drainage system work and the orbital surgery. "We didn't want to add any more volume into his orbit at that point," she said. "Because the patient was so swollen, we kept all of the patient's and donor's skin to close the wound."

Secondary procedures. Dr. Mardini had previously reconstructed the orbital floors with titanium plates, screws, and mesh following the initial trauma. "We removed all the material and reconstructed the orbital floors and medial walls with a synthetic implant about 6 months after the face transplant procedure," he said. During the secondary procedure, the surgical team also performed lacrimal drainage surgery and telecanthus and infraorbital nerve repairs and resected some excess skin, said Dr. Bradley.

One of the orbital implants elevated the patient's eye more than anticipated, however, producing hyperglobus and hypertropia. "We did a revision—a third surgery—to allow the eye to come down," she said. "It's important to note that strabismus surgery may be another necessary ophthalmological aspect."

Quality of Life

"In contrast to solid organ transplants, which are lifesaving, this is the ultimate quality-of-life surgery," said Dr. Bradley, alluding to both the transformative and challenging circumstances surrounding any face transplant. Three weeks after the first face transplant at Mayo Clinic, surgical team members surrounded the man who had tried to kill himself. Not yet able to talk, he scribbled on a notepad, "Far exceeded my expectations."

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Dr. Bradley is a consultant in the department of ophthalmology and oculoplastic surgeon at the Mayo Clinic and associate professor of ophthalmology at the Mayo Clinic College of Medicine and Science in Rochester, Minn. *Relevant financial disclosures: None.*

Dr. Grant is professor of surgery at the University of Maryland School of Medicine and oculoplastic surgeon, plastic surgeon, and chief of the division of plastic and reconstructive surgery at the R. Adams Cowley Shock Trauma Center at the University of Maryland Medical Center in Baltimore. *Relevant financial disclosures: None.*

Dr. Mardini is a professor of surgery at the Mayo Clinic College of Medicine and Science; consultant in the division of plastic surgery and director of the face transplant program at Mayo Clinic; and surgical director of Mayo Clinic's Essam and Dalal Obaid Center for Reconstructive Transplant Surgery in Rochester, Minn. *Relevant financial disclosures: None.*

For full disclosures, view this article at aao.org/eyenet.

EXTRA **MORE ONLINE.** For more images from the Mayo Clinic case, see www.flickr.com/photos/mayoclinic/albums/72157678243262502.

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Management of Submacular Hemorrhage

Submacular hemorrhage (SMH) is an uncommon complication of choroidal or retinal vascular abnormalities, including choroidal neovascularization (CNV), polypoidal choroidal vasculopathy (PCV), and retinal macroaneurysm. Of these, PCV is the condition most frequently associated with large SMH (reported in 20%-63% of eyes with PCV).

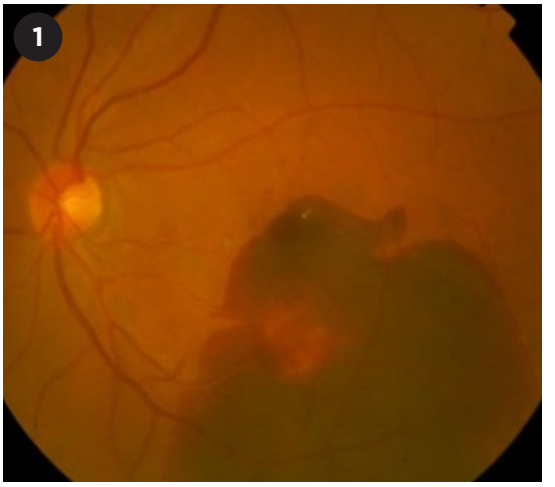
SMH can damage photoreceptors as a result of iron-induced toxicity, with irreversible retinal injury occurring as early as 24 hours after onset of the hemorrhage. Only 11% of eyes with SMH achieved a best-corrected visual acuity (BCVA) better than 20/200 after 2 years of observation.[1] Avery et al. found a mean loss of 3.5 lines of VA after 3 years in eyes with subfoveal hemorrhage secondary to exudative age-related macular degeneration (AMD), and almost half of these eyes (44%) had lost 6 or more lines.[2] The presence of subretinal CNV membranes predicts poorer final visual acuity.[3]

Diagnosis

Patients often present with decreased central vision, sometimes 20/200 or worse. On dilated fundus examination, SMH can be observed as an elevation of the neurosensory retina, which can also be associated with a hemorrhagic detachment of the retinal pigment epithelium (RPE; Fig. 1).

Subretinal versus sub-RPE. It is important to distinguish subretinal blood from sub-RPE blood, as hemorrhage at the subretinal level may be more harmful to photoreceptors. Clinically, subretinal blood may appear bright red, while sub-RPE blood appears darker. Optical coherence tomography (OCT) is a useful imaging tool for distinguishing the level at which hemorrhage has occurred. Yellowish-white depigmented blood or vitreous hemorrhage may also be present.

Seeking the cause. Although the underlying cause may be apparent on clinical examination, further imaging is often required to elucidate it. If the ocular media are sufficiently clear, fundus imaging should be performed with fluorescein angiography (FA) and indocyanine green angiography (ICGA) to identify and locate the primary pathology to guide treatment.



SUBMACULAR HEMORRHAGE. *Large SMH involving the fovea and extending beyond the inferotemporal vascular arcade.*

Treatment

Several monotherapy or combined approaches are used, including the following:

- Anti–vascular endothelial growth factor (anti-VEGF) monotherapy
- Pneumatic displacement (PD) + anti-VEGF therapy
- Intravitreal recombinant tissue plasminogen activator (rtPA) + anti-VEGF + PD
- Pars plana vitrectomy + subretinal injection of rtPA + subretinal or intravitreal PD

(See this article at aao.org/eyenet for a simple treatment algorithm.)

Anti-VEGF Therapy

Anti-VEGF monotherapy is a viable option for the treatment of SMH secondary to neovascular AMD or PCV. Studies evaluating anti-VEGF monotherapy have demonstrated robust visual outcomes, with 44% to 60% of eyes achieving 3 or more lines of VA improvement at 6 months.[4] One study showed that although eyes with thick SMH (>450 µm) achieved better visual

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outcomes with combination therapy, thinner SMH could be managed as effectively with anti-VEGF monotherapy.[5]

Choice of anti-VEGF. There is no evidence to suggest the superiority of one anti-VEGF agent over another in treating SMH. However, it should be noted that aflibercept has been shown to be cleaved by rtPA-induced plasmin in vitro, which might reduce the anti-angiogenic effect of aflibercept when combined with intravitreal rtPA for the treatment of SMH.

Pneumatic Displacement

PD utilizes intravitreal injection of an expansile gas to move blood away from the fovea. The procedure can be performed with or without intravitreal rtPA but is usually combined with intravitreal anti-VEGF therapy to treat the underlying pathology.

PD has been shown to be effective in displacing SMH, even without use of rtPA; for example, complete displacement was achieved in 80% of eyes within a week of treatment.[1] Moreover, it provides the added benefit of faster visual recovery compared with anti-VEGF therapy alone for the treatment of SMH secondary to PCV.[1]

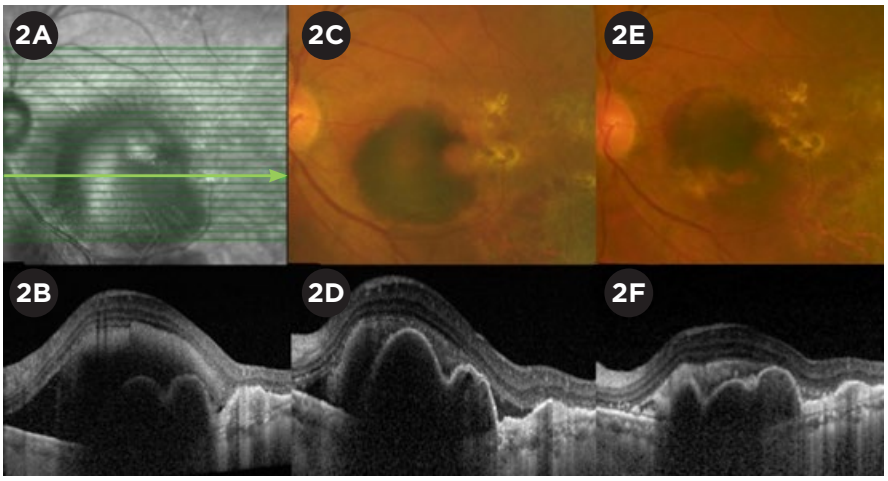
Adjunctive effects. By clearing thick blood away from underlying CNV membranes or polyps, PD can potentially enhance the action of anti-VEGF drugs (Fig. 2). In eyes with PCV, displacement of blood allows the physician to view the underlying polyps with ICGA (Fig. 3), thus facilitating treatment with either focal laser or photodynamic therapy (PDT).

Clinical considerations and caveats. Some important considerations should be discussed with the patient before proceeding with PD.

Positioning. Is the patient able to maintain the recommended facedown position for prolonged periods over several days?

Cataract. In phakic patients, PD can hasten the development or progression of cataract.

Intraocular pressure. Elevation of IOP can occur in the ensuing days and up to 1 or 2 weeks after the procedure, depending on the gas injected. Thus, IOP should be monitored closely, and PD should be used with caution in patients with preexisting glaucoma.



PRESENTATION AND TREATMENT. *(2A) Near-infrared fundus image shows a large SMH involving the fovea. The green arrow indicates the position of the OCT line scan. (2B) OCT shows subretinal hemorrhage and RPE detachments partially obscured by blood. (2C) Fundus photo shows a decrease in size of the SMH 1 week after PD and intravitreal aflibercept injection. (2D) OCT shows a reduction in amount of subretinal hemorrhage. RPE detachments are now clearly visible. (2E) Fundus photo shows further reduction in SMH 1 month after treatment. (2F) OCT shows marked reduction in subretinal hemorrhage and a decrease in height of RPE detachments 1 month after treatment.*

Location of SMH. The gas can inadvertently shift more subretinal blood toward the fovea, especially if most of the hemorrhage lies in the superior macula.

How to perform PD. This procedure can be performed in the outpatient setting in a clean room under sterile conditions and topical anesthesia. If rtPA or anti-VEGF therapy is planned, these agents should be administered prior to gas injection.

Either SF_6 or C_3F_8 gas can be used. The gas is drawn into a 3-mL syringe without dilution and injected with a 25-gauge needle via the pars plana into the vitreous cavity. After the injection, VA should be assessed with counting fingers, and anterior chamber paracentesis is performed as required.

After treatment. The patient is advised to remain in a facedown position as much as possible for a few days. The patient should return the day after PD for a dilated fundus examination and IOP check, with similar follow-up occurring at 1 week and at monthly intervals thereafter, depending on subsequent treatment.

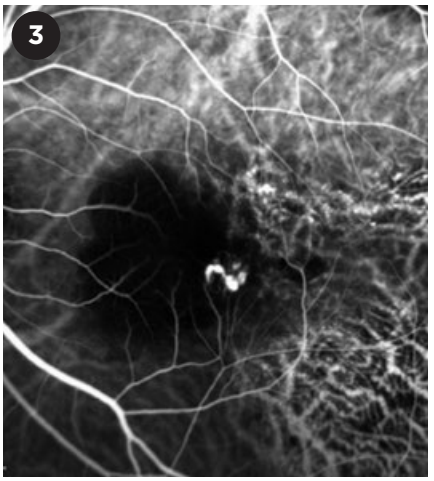
Recombinant Tissue Plasminogen Activator

rtPA is an enzyme that catalyzes the conversion of plasminogen to plasmin, the main enzyme involved in clot breakdown. Several studies evaluating injection of rtPA combined with PD have reported visual acuity gain of 3 lines or more in 42% to 66% of eyes.[6]

It can be administered as a subretinal injection or injected into the vitreous cavity for the lysis of submacular blood clots. Intravitreal injection of rtPA is the less invasive, less time consuming, and less technically challenging of these approaches. Studies have confirmed that rtPA injected intravitreally can migrate across the vitreous cavity and the retina into the subretinal space.[7]

Reported rates of complete SMH displacement and short-term visual outcomes are similar between subretinal injection of rtPA and intravitreal rtPA with PD.[8]

Adverse effects of rtPA. Ocular side effects of rtPA include photoreceptor cell loss, RPE pigmentary changes, and exudative retinal detachment. These effects appear to be dose dependent, and a dosage of less than 25 µg/0.1 mL is recommended to avoid them. Also,



PCV POLYPS. *ICGA image shows juxtafoveal polyps appearing in a stringlike configuration.*

injection of rtPA into a gas-filled eye (which concentrates the drug at the retinal surface) and repeat injections should be avoided.

Hemorrhagic. rtPA can cause hemorrhagic complications, an important consideration if rtPA is to be given within 72 hours of bleeding onset. (It should be noted, however, that breakthrough vitreous hemorrhage can also occur regardless of the treatment, and patients should be made aware of this during the informed consent process.)

Although there have been no reports of systemic side effects with these low intraocular doses, the possibility of systemic hemorrhagic complications should not be forgotten, especially in susceptible patients, such as those on anticoagulants.

Vitrectomy

If vitreous hemorrhage is present, pars plana vitrectomy facilitates its removal, which improves fundus visualization for monitoring treatment response and allowing subretinal injection of rtPA. The procedure usually involves a combination of small-gauge vitrectomy, subretinal injection of rtPA using a 41-gauge flexible cannula, and treatment of the underlying pathology with laser or anti-VEGF, followed by fluid-air exchange and intravitreal gas tamponade with nonexpansile SF_6 or C_3F_8.

Subretinal PD. Subretinal PD, in which air is injected into the subretinal space, has been described as an alternative to PD with intravitreal gas. The higher pressure exerted by subretinal air may be more effective in displacing the subretinal blood clot after rtPA-assisted clot lysis compared with intravitreal gas tamponade.

Subretinal PD eliminates the need for prolonged facedown positioning and the risk of gas-related IOP elevation, but it may be associated with higher risk of macular hole formation.[9,10]

Study results. In a review of 38 studies, Van Zeeburg et al. found no clear difference in complete displacement of SMH or complication rate between vitrectomy with subretinal injection of rtPA versus intravitreal rtPA with PD without vitrectomy.[11]

Hirashima et al. reported the results of rtPA-assisted vitrectomy, gas tamponade, and postoperative treatment with intravitreal ranibizumab or PDT, demonstrating a visual improvement of 3 lines or more in 66% of eyes.[12] These results compared favorably with other groups using a similar surgical technique.[13-15]

Possible downside. A potential disadvantage of vitrectomy is the rapid washout of anti-VEGF agents in vitrectomized eyes, which may necessitate more frequent intravitreal injections in patients with CNV or PCV.

Management of the Underlying Pathology

FA, ICGA, and OCT angiography are essential imaging modalities in diagnosing the underlying cause of SMH and in selecting and monitoring the subsequent treatment.

Macroaneurysms. These vascular abnormalities can be adequately managed with focal thermal laser photocoagulation.

CNV. Intravitreal anti-VEGF remains the gold standard for treatment of CNV.

PCV. Management of PCV depends on its location. Subfoveal and juxtafoveal PCV can be treated with anti-VEGF as monotherapy or in combination with PDT. Combined therapy may help to quickly close the polypoidal lesions and facilitate resolution of SMH, but it carries the risk of RPE tear. Deferring PDT until most of the blood has resorbed allows better visualization of underlying polyps and reduces attenuation of laser energy.

Extrafoveal PCV can be managed effectively with anti-VEGF in combination with either focal thermal laser photocoagulation or PDT.

Conclusions

As a general approach to SMH treatment, PD can be combined with intravitreal rtPA if there are no contraindications. In addition, anti-VEGF therapy should be administered as indicated by the underlying pathology. Although SMH can be challenging to manage, reasonable visual outcomes can be achieved with timely and appropriate intervention.

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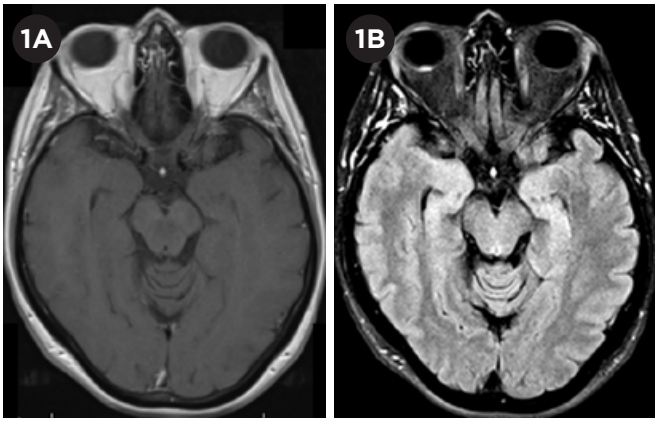
The Mystery Choroidal Lesion

Tabitha Tisch* was anxious. The 53-year-old woman had been struggling to cope with a number of health conditions—including myasthenia gravis, hyperthyroidism, and fibromyalgia—but this was different. At home, one Saturday morning, she was struggling to find words, had episodic diplopia, and was experiencing difficulty typing. This resolved a few hours later, but since she had never experienced something like this before, she rushed to the nearest emergency department.

Given the concern for a cerebrovascular event, magnetic resonance imaging (MRI) of the brain was performed, which was normal except for incidental thickening along the posterior aspect of the right globe (Figs. 1A and 1B).



MRI. *(1A) T1 and (1B) FLAIR sequences reveal slight focal thickening along the posterior aspect of the right eye, most noticeable on FLAIR. No other obvious mass lesions were noted in either orbit, and the optic nerve sheaths were unremarkable. The mass appeared isointense to the vitreous on T1-weighted imaging and hyperintense on FLAIR.*

First Impressions

Shortly after her ER visit, Ms. Tisch was referred to our ophthalmology clinic. Her vision was 20/20 in both eyes, her pupils were equally reactive without an afferent pupillary defect (APD), and her intraocular pressure (IOP) was 8 mm Hg in both eyes. The anterior segment examination was normal.

Although the fundus exam of the left eye was unremarkable, the right eye revealed an elevated, well-circumscribed, ovoid lesion with an underlying orange hue. It was superior to the optic disc measuring 5 × 6 mm in diameter (Fig. 2A, arrow).

On ultrasonography, the lesion was acoustically solid with medium-to-high internal reflectivity on A-scan (Fig. 2B). Enhanced-depth imaging optical coherence tomography (EDI-OCT) showed elevation of the retina by a hyporeflective choroidal mass, with some attenuation of the overlying photoreceptor layers, minimal posterior shadowing, and visible vessels (Figs. 2C and 2D). The mass demonstrated no intrinsic hyper- or hypoautofluorescence on fundus autofluorescence, but it did show increasing hyperfluorescence on fluorescein angiography (FA) that increased in intensity and faded during recirculation (Figs. 2E and 2F). Indocyanine green angiography (ICGA) demonstrated early hypercyanescence with late "washout" isocyanescence (Figs. 2G and 2H).

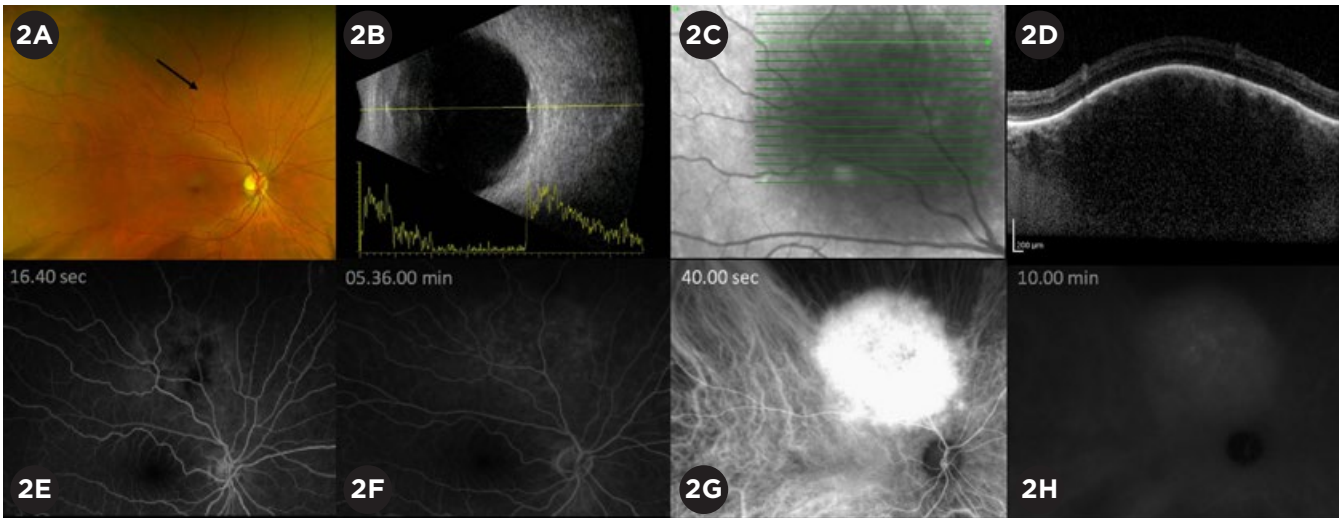
Making the Diagnosis

Our differential for an amelanotic, elevated choroidal lesion in an asymptomatic patient consisted of a choroidal hemangioma, choroidal granuloma, amelanotic choroidal melanoma, or a metastasis.

Compared with amelanotic choroidal melanomas, choroidal hemangiomas tend to have a more reddish-orange hue on funduscopic examination. Additionally, on A-scan, choroidal hemangiomas typically demonstrate high reflectivity, unlike choroidal melanomas, which more frequently have low internal reflectivity.

Our suspicion for metastatic disease was low in Ms. Tisch given the clinical appearance of a solitary, unilateral lesion in a patient without a prior cancer history or associated symptoms. Thus, the reddish hue to this choroidal lesion coupled with the findings on EDI-OCT, FA, and ICGA were all consistent with a diagnosis of circumscribed choroidal hemangioma.

BY **MEGAN ROWLANDS, MD, MPH, IRINA BELINSKY, MD,** AND **YASHA S. MODI, MD.** EDITED BY STEVEN J. GEDDE, MD.



FURTHER IMAGING. *(2A) Although difficult to appreciate on this fundus photo, examination of the right eye revealed an elevated, deep mass with a reddish hue superior to the disc and arcades (arrow). (2B) Combined B- and A-scan of the right eye showed an elevated choroidal lesion with medium-to-high internal reflectivity. (2C, 2D) EDI-OCT raster scan showed a hyporeflective choroidal mass elevating the overlying retina with posterior shadowing. (2E) FA showed increasing hyperfluorescence corresponding to the choroidal lesion that increased in intensity through 1 minute (2F) but faded subsequently in the late phases of the FA. (2G) ICGA demonstrated early hypercyanescence with (2H) late "washout" isocyanescence.*

Discussion

Choroidal hemangiomas are benign vascular tumors typically diagnosed between the second and fourth decades of life. Most patients are asymptomatic until adulthood but can then develop blurred vision or hyperopic shifts from the anteriorly displaced retina or secondary serous retinal detachments.

Choroidal hemangiomas are classified as either circumscribed or diffuse. As the name implies, circumscribed hemangiomas appear as discrete, well-delineated tumors with a reddish hue and are typically located in the macula or peripapillary region.

Conversely, diffuse hemangiomas are more extensive within the choroid and can be associated with nonocular hemangiomas elsewhere, such as the skin, central nervous system, and in certain systemic angiomatous disorders (like Sturge Weber syndrome). They can also be associated with ipsilateral glaucoma. Given their associated ocular and systemic manifestations, diffuse choroidal hemangiomas tend to be detected in younger patients.[1]

Imaging

Various modalities can be used to further characterize choroidal hemangiomas.

FA. On FA, choroidal hemangiomas characteristically show linear areas of hyperfluorescence in the early arterial phases followed by diffuse leakage in the later arterial and venous phases.

ICGA. On ICGA, choroidal hemangiomas typically demonstrate a lacy, diffuse pattern of hypercyanescence in the early phases followed by washout of the cyanescence within the tumor.[1]

MRI. Use of MRI is not always helpful in differentiating choroidal tumors, especially when they are too small to visualize and evoke a signal, but it can be complementary to ophthalmic imaging in the setting of diagnostic uncertainty. Choroidal hemangiomas are hyperintense to vitreous on T1 and isointense on T2.[2] In our case, the hemangioma was not well identified on either sequence, which may in part be due to its small size of < 2 mm thickness on ultrasonography. It was most conspicuous and hyperintense on T2–fluid attenuated inversion recovery (FLAIR) imaging. Damento et al. recently highlighted the utility of T2-FLAIR sequence for increased conspicuity and identification of certain choroidal tumors, including uveal melanoma and choroidal hemangioma, both of which show T2-FLAIR hyperintensity.[3]

Frequent misdiagnoses. Even with these characteristic imaging findings, differentiating between choroidal hemangiomas and other choroidal lesions, namely choroidal melanomas, remains challenging, and these tumors can often be misdiagnosed.[4]

EDI-OCT shows promise. In a review of various choroidal tumors imaged with EDI-OCT, several key features were noted. All choroidal melanocytic tumors—for example, choroidal nevi, choroidal melanomas, and optic disc melanocytomas—displayed a band of high reflectivity with posterior shadowing. By comparison, choroidal hemangiomas demonstrated low to medium reflectivity, and choroidal metastases were typically low in reflectivity. In addition to the differing degrees of reflectivity, the lesions differed in terms of the appearance of adjacent photoreceptor layers. For example, choroidal melanocytomas and choroidal nevi demonstrated loss of the overlying photoreceptor layers, whereas the choroidal melanomas, hemangiomas, osteomas, and metastases displayed "shaggy" photoreceptor layers.[5] Also, the choroidal vessels are usually visible on EDI-OCT of choroidal hemangiomas, while they tend to be compressed and not visible in the case of choroidal melanoma.

Treatment

Treatment of choroidal hemangiomas depends on the severity of symptoms and presence of retinal detachment. Asymptomatic patients do not require treatment but rather can be observed. In symptomatic cases, hemangiomas may be treated with photodynamic therapy (PDT), photocoagulation, external beam radiation, or transpupillary thermotherapy. PDT is the preferred treatment, particularly for lesions that involve the macula. Intravitreal anti–vascular endothelial growth factor (VEGF) treatments and oral propranolol have also been used successfully in some cases to resolve associated subretinal fluid.[6,7]

Patient's Course

Because Ms. Tisch remained asymptomatic with stable vision and without the presence of subretinal fluid or detachment, we decided to observe her. A comprehensive workup of her transient neurologic symptoms was negative, and her symptoms did not recur. We advised her to monitor for any visual changes, including blurred vision and metamorphopsia, and we plan to see her again in 3 months for a repeat dilated exam and EDI-OCT.

* Patient name is fictitious.

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Relevant financial disclosures: None.

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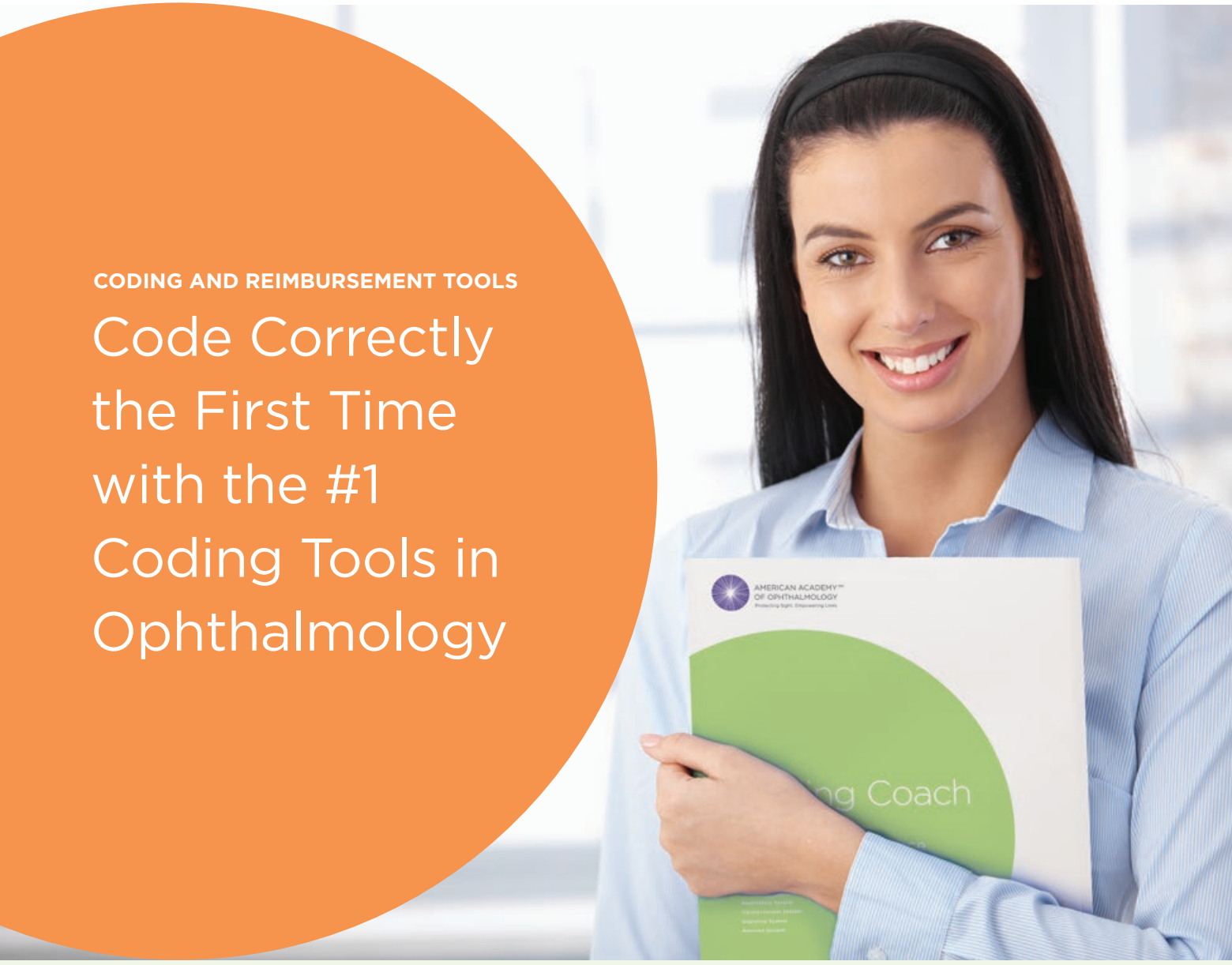

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the full US Prescribing Information for LUXTURNA on the following pages

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

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1 INDICATIONS AND USAGE

LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities

Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure

Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles

Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract

Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

8.5 Geriatric Use
The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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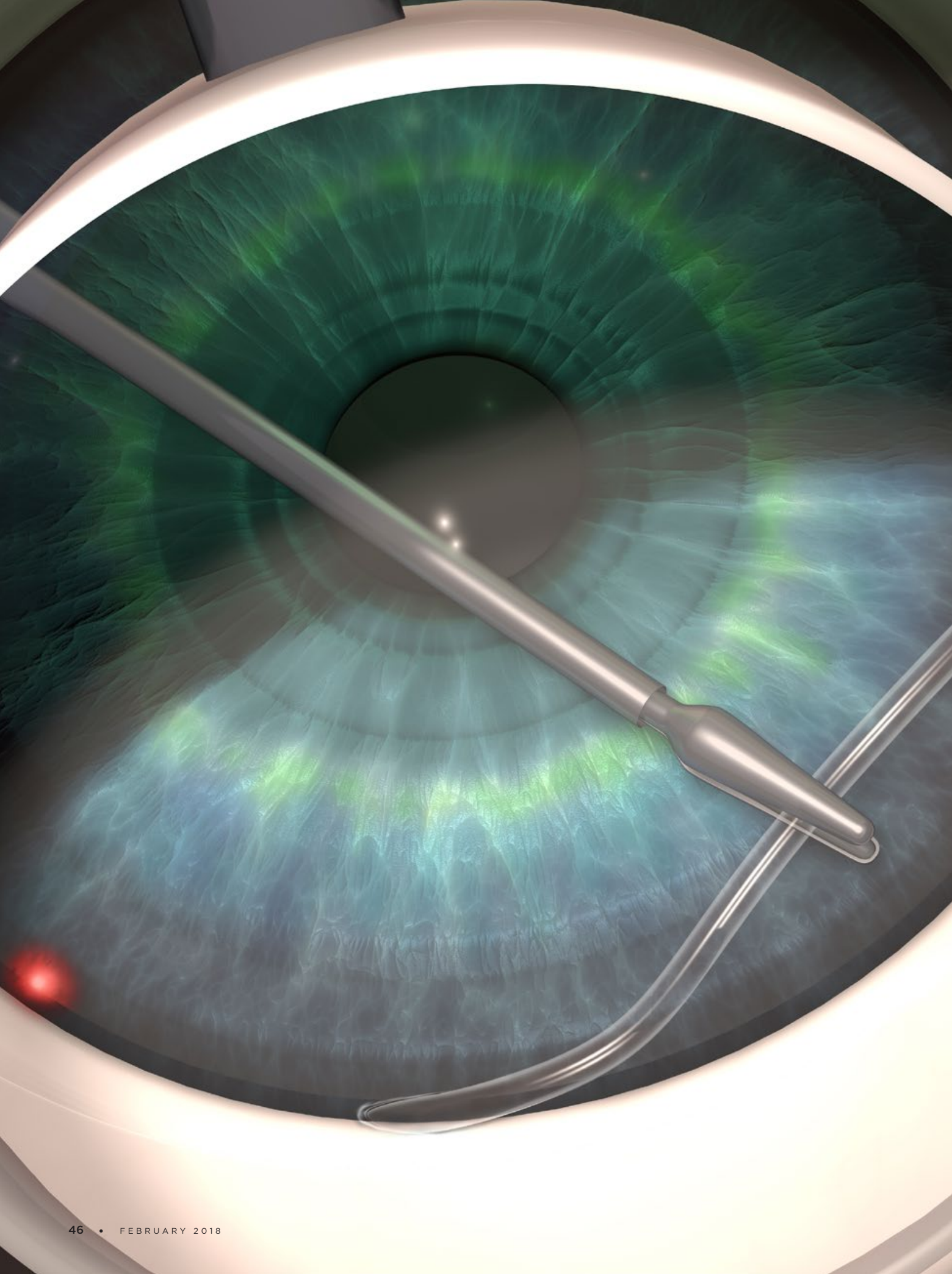


MIGS: Expanding Options for Glaucoma Treatment

As the uptake of MIGS continues to increase, early adopters share their perspectives and practices.

By Lori Baker-Schena, MBA, EdD, Contributing Writer

In the decade since Iqbal Ike K. Ahmed, MD, coined the term *microinvasive glaucoma surgery*—better known as MIGS—the field has grown exponentially.

Dr. Ahmed noted several reasons for the growing interest in MIGS: "Compliance is really poor in glaucoma patients, and even if the patient is compliant, quality of life and the high costs of medicine continue to be issues. We must continually look for solutions for these patients. MIGS are moving in that direction," said Dr. Ahmed, who is a glaucoma specialist with the Prism Eye Institute in Mississauga, Ontario, Canada.

An online survey of glaucoma surgery practice preferences conducted by the American Glaucoma Society found that among patients who had initial surgery for primary open-angle glaucoma (POAG), the percentages were 59% for trabeculectomy with mitomycin C (MMC), 23% for a glaucoma drainage device (GDD), and 14% for MIGS. When the glaucoma procedure was combined with cataract surgery, the percentages were as follows: trabeculectomy with MMC, 24%; MIGS, 22%; and GDD, 9%.[1]

The survey also found that iStent and Trabectome were the most commonly used MIGS procedures in 2016.

Debating the Role of MIGS

Although multiple studies have associated MIGS with a favorable safety profile and modest efficacy, others cite a lack of evidence in proving the effectiveness of these techniques.

In response to "good, healthy skepticism" from some quarters, Dr. Ahmed said that "MIGS have been very well studied for many years, with a wealth of published data." He emphasized that MIGS are not designed to replace trabeculectomy in advanced glaucoma. Rather, "Surgeons are using MIGS procedures in their mild to moderate patients who need lower intraocular pressure (IOP) but in whom they are reluctant to operate because of the side effects associated with trabeculectomy."

The Case for MIGS

Glaucoma specialist John P. Berdahl, MD, with Vance Thompson Vision in Sioux Falls, South Dakota, said he considers the entire range of MIGS options when tailoring treatment for his glaucoma patients.

Fitting the procedure to the patient. "It is my duty to fit the procedure to the patient," Dr. Berdahl noted. "That being said, when you are first starting out with MIGS, it is good to get comfortable with one procedure and then expand out to other procedures because there are a lot of similarities." He added that the learning curve for a MIGS procedure is between 10 and 20 cases.

Dr. Berdahl discussed his 3-year results from patients who had an iStent implanted in combination with cataract surgery.[2] "This approach effectively lowered IOP in open-angle glaucoma (OAG) patients from a mean of 19.13 ± 6.34 mm Hg to 15.17 ± 3.53 mm Hg after 2 years," he said. "Interestingly, we found that the magnitude of IOP reduction was more significant in patients

Alfred T. Kamajian

with higher preoperative pressure and also that medication use was significantly reduced."

An "early adopter's" experience with iStent. Glaucoma specialist Mark J. Gallardo, MD, of El Paso Eye Surgeons in Texas, is an "early adopter" of several MIGS procedures, an interest fueled by his desire to provide patients with the most advanced technology, especially if it proves safer, with a quicker recovery.

Dr. Gallardo believes that the modest results from the early clinical trials of the iStent do not reflect the full potential of this approach, as the trial investigators were the first in the world to use the device in a clinical setting and had minimal experience in the best placement. He noted that 70% of the stents were implanted by surgeons who had performed 5 or fewer procedures.

"The learning curve, as well as the previous lack of knowledge on how to maximally manipulate the outflow system with targeted stent implantation, adversely impacted the data," he said.

Placement and patients. Ultimately, surgeons, including Dr. Gallardo, learned that targeting areas adjacent to collector channels could enhance the efficacy of the stent. Intraoperative visual cues, such as increased regurgitation of blood (blotching) within Schlemm's canal or increased areas of pigmentation on the posterior trabecular meshwork, help to highlight the location of patent collector channels.

"This, coupled with our identification of ideal candidates for the procedure—those already on 1 to 3 glaucoma drugs with IOP targets in the mid-teens range—have led to results superior to those of the pivotal trial, and subsequent research has demonstrated the safety and effectiveness of the trabecular microbypass stent [iStent]," he said.

Case series shows benefits. Dr. Gallardo conducted a retrospective case series in a predominantly Hispanic patient population with moderate to severe glaucoma to assess reduction of IOP and/or medication burden at 12 months following implantation of 1 trabecular microbypass stent during cataract surgery.[3]

A MIGS Primer

MIGS procedures share 5 key characteristics[1]:

- Ab interno microincision through a clear corneal approach, allowing MIGS to be performed easily in conjunction with cataract surgery; providing a direct view of the angle; and avoiding conjunctival scarring, in case later glaucoma surgery is required.
- Minimal trauma, maintaining normal ocular anatomy and function as much as possible.
- At least modest efficacy, making them a reasonable option in selected patients.
- Favorable safety profile, avoiding the serious complications seen with traditional surgeries, including bleb infections, hypotony, and corneal decompensation.
- Rapid recovery, reducing the impact on patients' quality of life.

Implanted MIGS

Stent devices fall into 3 main categories:

1. Increasing trabecular outflow:

- **iStent (Glaukos).** Implanted in the trabecular meshwork, the stent allows aqueous humor to flow fron the anterior chamber into Schlemm's canal (FDA approved in 2012).

Glaukos recently received approval for a pivotal U.S. trial of the iStent SA system (consisting of 2 stents in a single inserter) as a standalone procedure in pseudophakic patients.

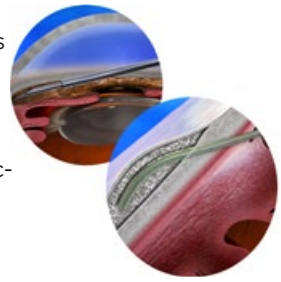
- **Hydrus Microstent (Ivantis).** Described as an intracanalicular scaffold, this 8-mm-long device is inserted into Schlemm's canal to establish outflow (approved in Europe but not in the United States or Canada).

2. Targeting the suprachoroidal space:

- **CyPass Micro-Stent (Alcon).** This device, implanted in the supraciliary space, allows suprachoroidal aqueous outflow (FDA approved in 2012).

3. Opening a subconjunctival filtration pathway:

- **XEN 45 Gel Stent (Allergan).** This soft, collagen-derived gel device creates a new pathway for aqueous flow from the anterior chamber into an ab interno bleb in the subconjunctival space (FDA approved in 2016).



Nonimplant MIGS

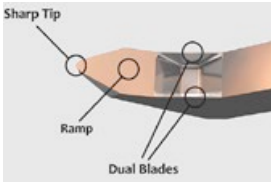
- **Trabectome (NeoMedix).** Electrocautery, irrigation, and aspiration are used to selectively ablate the trabecular meshwork and the inner wall of Schlemm's canal to allow aqueous free access to the canal and its collector channels (FDA approved in 2004).
- **Kahook Dual Blade (New World Medical).** This relatively inexpensive single-use disposable handpiece employs 2 parallel blades to remove a strip of trabecular meshwork to im-

Results of the entire cohort showed that IOP was reduced from 16.5 mm Hg preoperatively to 12.9 mm Hg, and the mean number of medications decreased from 2.3 to 0.9.

Reducing medication burden. "At 12 months, 94% of all eyes achieved their predefined treatment goal of reduced IOP and/or medications," Dr. Gallardo noted. Among patients who had medically controlled glaucoma entering cataract surgery plus stent implantation, 69% were able to completely eliminate their need for medications. Of this latter group, 55% had been on 3 or more medications preoperatively, he said.

"The earlier we use MIGS, the less we need to rely on medications," Dr. Gallardo said.

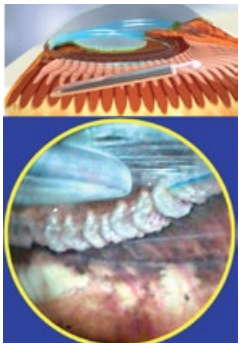
He noted several benefits from reducing a patient's medication burden: increased compliance, lower monthly costs (generic drugs are skyrocketing in price), and less exposure to the preservative benzalkonium chloride, which has been associated with ocular surface disease and damage to endothelial cells in the trabecular columns.



prove outflow, without need for an expensive electrocautery or irrigation/aspiration system.

• **Gonioscopy-assisted transluminal trabeculotomy.** GATT is a minimally invasive ab interno circumferential trabeculotomy (see Fig. 1, next page) that is performed through two 1.0-mm corneal incisions and employs either a microcatheter, 5-0 Prolene suture, or TRAB 360 handpiece (Sight Sciences). After cannulation, the entire trabecular meshwork is unroofed.

• **Ab interno canaloplasty (ABiC).** The procedure, performed through a single self-sealing clear corneal incision, involves 360-degree viscodilation of the canal using either the iTrack microcatheter (Ellex) or the VISCO360 (Sight Sciences) handpiece and an ophthalmic viscoelastic device inserter.



• **Endoscopic cyclophotocoagulation (ECP).** An endoscopic probe is inserted via a corneal or pars plana incision to ablate a selected portion of the ciliary epithelium under direct endoscopic visualization. This process decreases aqueous production.

1 Saheb H, Ahmed IK. *Curr Opin Ophthalmol.* 2012;23:96-104.

ABiC: Impact on Practice

Dr. Gallardo also performs ab interno canaloplasty (ABiC), or transluminal viscodilation, which aims to improve outflow by dilating Schlemm's canal 360 degrees through a small corneal incision, using a microcatheter and viscoelastic.

Pearls for ABiC. He makes the temporal clear corneal wound directly across from the nasal angle with side-port incisions at a 90-degree angle. He recommends avoiding the limbal vessels as much as possible, as surface bleeding can stain the viscoelastic used as a coupling agent for the gonioscope and obstruct the view of the drainage angle.

Dr. Gallardo uses the iTrack catheter, which, he said, "provides tactile feedback on the patency or health of the canal during circumnavigation, while the illuminated tip allows me to track the catheter's movement, providing me assurance that I am actually in the canal and not in the suprachoroidal space."

What about moderate to severe glaucoma? Dr. Gallardo said that the advent of MIGS has had an enormous impact on his practice, not only in his treatment of patients with mild glaucoma but also in those with moderate to severe glaucoma.

"Whether [they are] performed as a standalone procedure or as an adjunct to cataract surgery, I have found these microinvasive procedures very effective at meeting my patients' needs," he said. "In patients requiring further reduction in IOP, I try a MIGS procedure or a combination of MIGS procedures before filtering, in most but not all circumstances." He added, "I was doing 8 to 10 filters a week, and now I perform 1 ab externo filtration every 4 to 6 weeks."

GATT: A New Twist on Trabeculotomy

While ABiC is a minimally invasive approach to canaloplasty, gonioscopy-assisted transluminal trabeculotomy (GATT) is a minimally invasive modification of standard trabeculotomy.

"When I was a medical student, I felt that trabs and tubes seemed really harmful to the eye, and I kept questioning why we were doing what we were doing," said glaucoma specialist Davinder S. Grover, MD, MPH, of the Glaucoma Associates of Texas in Dallas.

"I started practice right around the time the iStent was being investigated," Dr. Grover added. "My partners and I were primary investigators on the CyPass microstent, Hydrus, and XEN gel stent. Additionally, Dr. Ronald L. Fellman and I were developing techniques of our own (ab interno bleb revision and ab interno Ex-PRESS shunt removal), and all this research converged to provide a productive environment for our own innovations."

Development of GATT. Drs. Grover and Fellman

(along with their colleagues Drs. David Godfrey and Oluwatosin Smith) developed the GATT procedure, an ab interno circumferential trabeculotomy that is performed through 2 corneal incisions, 1 mm each. A small goniotomy is created, and a microcatheter or 5-0 Prolene suture is used to cannulate 360 degrees of Schlemm's canal and then unroof the entire trabecular meshwork (Fig. 1).

Dr. Grover said a major advantage of this procedure is that the entire drainage system is accessed, rather than just a small portion. In addition, it spares conjunctival tissues from incision and scarring, allowing better outcomes if traditional glaucoma surgery is required later.

Findings from 2 studies. In the first study, "we looked back at our 2-year data on 10 patients (14 eyes) under 30 years old with a dysgenic anterior segment angle and uncontrolled primary congenital glaucoma or juvenile open-angle glaucoma who underwent GATT," Dr. Grover said. "They experienced a mean decrease in IOP from 27.3 to 14.8 mm Hg and a mean decrease in meds from 2.6 to 0.86.[4]

"Moreover, when we evaluated GATT outcomes in 198 patients with POAG and secondary open-angle glaucoma (SOAG), either isolated or combined with cataract surgery, we found very encouraging results that were similar to if not better than previously published data on ab externo circumferential trabeculotomy," Dr. Grover said.

The patients in this study with POAG had an average IOP decrease of 9.2 mm Hg (a mean reduction of 37.3%) at 24 months, with an average decrease of 1.43 glaucoma medications.

At that same time point, the SOAG patients had an average decrease in IOP of 14.1 mm Hg (a mean reduction of 49.8%) on an average of 2.0 fewer medications.[5]

Learning from failure. While Dr. Grover was pleased with the results, he gained greater insight from the treatment failures. In the POAG group, there was a correlation between mean deviation (MD) in visual field defect parameters and outcomes: Patients with a worse MD had a higher chance of treatment failure in the first 3 months.

"This is suggestive of the health of the eye's inherent drainage system," Dr. Grover said. "Since it is difficult to visualize the collector channels and episcleral vasculature, we searched for other indicators that would serve as a proxy to determine the patency of the outflow system."

The wave as an indicator. In seeking such a proxy, Drs. Fellman and Grover drew on their experience with an earlier MIGS, Trabectome. During that type of surgery, they had observed a nasal perilimbal and/or episcleral vessel wave of fluid adjacent to the trabeculotomy site. "We believe this fluid wave, which we named an episcleral venous fluid wave (EVFW), signifies intraoperative structural patency of the conventional outflow system and is a sign that the collector system is at least anatomically functional."[6]

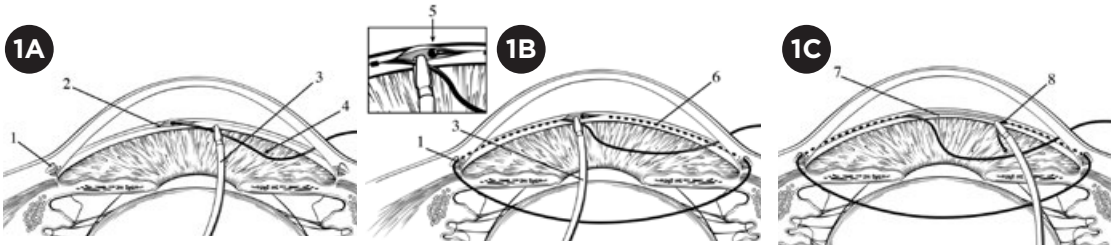
Dr. Grover said the presence or absence of this EVFW could be a prognostic indicator for success after a Trabectome surgery. In a study of 68 eyes of 49 patients with glaucoma who underwent phaco plus Trabectome or Trabectome alone, the eyes with a poorly defined EVFW had a higher likelihood of further glaucoma surgery.[7]

He uses the EVFW as a prognostic sign for GATT as well. "When I perform a GATT and I see an EVFW, I am very optimistic about that surgery."

Combined MIGS Procedures

One of the hot topics at the American Glaucoma Society's 2017 annual meeting was combining MIGS procedures. Won I. Kim, MD, a glaucoma specialist with Walter Reed National Military Medical Center in Bethesda, Maryland,* gave a presentation suggesting that multiple MIGS procedures can be successfully combined without significant additional risk.

Dr. Kim said, "Because of their relatively modest efficacy, MIGS procedures have traditionally been



KEY STEPS IN GATT. *(1A) Initial cannulation of Schlemm's canal. (1B) The microcatheter (or suture) has been passed 360 degrees around the canal. (1C) The distal tip of the catheter/suture has been retrieved and is being externalized, creating the circumferential trabeculotomy. KEY: 1, Schlemm's canal (SC); 2, initial goniotomy site; 3, microsurgical forceps; 4, either the microcatheter or suture; 5, distal end of the catheter/suture after it has been passed around SC; 6, path of the catheter/suture within SC; 7, trabecular shelf created by this procedure; 8, trabeculotomy resulting from GATT.*

Grover DS et al. *Ophthalmology.* 2014;121(4):855-861.

limited to mild to moderate disease; but perhaps combined MIGS procedures, with their potentially improved efficacy, can be extended to include those with severe disease."

Mix-and-match MIGS. Dr. Kim has been mixing and matching MIGS procedures, based on specific patients' needs. One of these combinations is ab interno trabeculectomy plus ABiC.

"My approach was removing a section of trabecular meshwork with the Trabectome or Kahook Dual Blade and then viscodilating the rest of Schlemm's canal 360 degrees with the iTrack," Dr. Kim said (Fig. 2). "This could take advantage of the different mechanisms of both sectoral trabecular meshwork removal and canaloplasty while simultaneously addressing their weaknesses," such as the limited sectoral aspect of Trabectome and the residual trabecular meshwork resistance after canaloplasty.

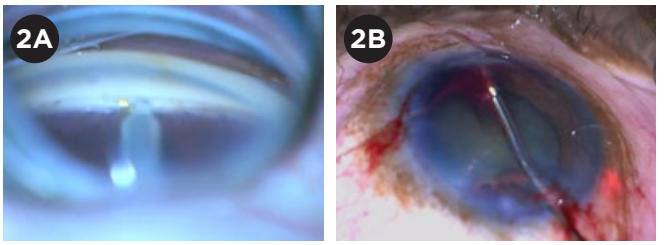
He has also successfully used several other multitechnique approaches. These include ABiC combined with micropulse transscleral cyclophotocoagulation (TSCPC; Fig. 3), trabecular meshwork bypass (using either iStent, GATT, or Trabectome) combined with endoscopic cyclophotocoagulation (ECP; Fig. 4), and CyPass supraciliary stent combined with trabecular meshwork bypass (using iStent or Kahook Dual Blade; Fig. 5).

He said that in his experience, all of these techniques have shown the ability to lower IOP into the low-teens range, reduce medication burden, maintain an excellent safety profile, and allow for rapid visual recovery.

Multi-MIGS plus phaco. Dr. Berdahl is also an advocate of combined MIGS. He compared the outcomes of combined microbypass stent implantation, cataract extraction, and ECP to those obtained with just the microbypass stent and concomitant cataract surgery in patients with OAG.[8]

He found that patients who underwent the combined approach experienced a mean IOP reduction of 7.14 mm Hg compared with 4.48 mm Hg in the control patients who did not have ECP. He found that the combination procedure was also effective in patients with severe OAG.

"The combined approach makes sense," Dr. Berdahl said. "We are trying to avoid the morbidity of more aggressive glaucoma surgeries. The question then becomes whether the efficacy is good enough. My approach is safety first and efficacy second. I will try the MIGS first."



TRABECTOME + ABIC. *(2A) Trabectome is used to remove a sector of trabecular meshwork. (2B) ABiC is performed through the Trabectome's ablation zone.*

MIGS Caveats

Steven L. Mansberger, MD, MPH, of the Devers Eye Institute in Portland, Oregon, has closely watched the advent of MIGS. He expressed concerns in the areas of efficacy and costs.

"As a glaucoma specialist, I am always interested in finding new ways of lowering pressures safely and effectively, and I applaud the investigators in this space," Dr. Mansberger noted.

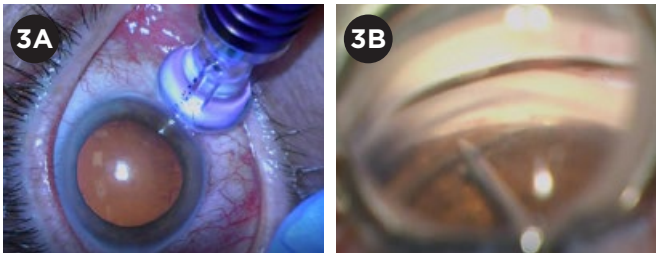
"That being said," he added, "MIGS may be useful for some patients, but traditional surgeries are required by the vast majority of surgical glaucoma patients, and it is imperative that we continue to learn the ins and outs of trabs and tubes in our glaucoma fellowships."

Efficacy concerns. Dr. Mansberger pointed out that some MIGS such as the iStent make only a millimeter of difference in IOP, and "we do not understand the characteristics of patients who most benefit from MIGS above and beyond cataract surgery alone."

Dr. Mansberger recounted a number of earlier implant devices that had failed, including several limbal and suprachoroidal stents in the 1950s and 1960s, and a XEN-like implant in the 1980s.[9]

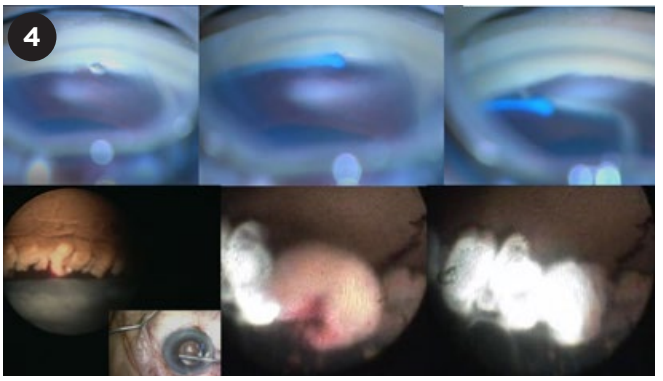
"We have new modifications such as mitomycin C [e.g., with XEN implants]," he added. "But time will tell if these new MIGS will be more effective or if history will repeat itself."

Cost factors. The downside of many of the MIGS surgeries is their cost, Dr. Mansberger pointed out. MIGS such as iStent, XEN, and Trabectome can add up to $4,000 to the cost of cataract surgery alone when factoring in surgeon charges, device costs,



TSCPC + ABIC. *(3A) After micropulse TSCPC is completed, (3B) ABiC is performed.*

Won I. Kim, MD



GATT + ECP. *(4) TRAB 360 handpiece is used to perform GATT, which is followed by ECP.*

anesthesia costs, and surgical center fees. "We need to look at changing the cost-benefit ratio in terms of costs," Dr. Mansberger said.

On the other hand, he noted that the GATT procedure is one of the most cost-effective MIGS—it can be done using a $5 suture. "And Dr. Grover has shown good results 2 to 3 years out, making this the approach to watch," Dr. Mansberger said.

Multiple surgeries? He also has concerns about patients who may need subsequent surgeries if a MIGS procedure does not effectively lower IOP.

"In most patients we see who can't use their drops or who have severe glaucoma, we do a traditional procedure, and we only need to operate one time to treat the problem. That is preferable to multiple surgeries," he said.

"Down the road, MIGS will be considered based on cost, IOP response, and visual field outcomes," said Dr. Mansberger. "Through the efforts of these MIGS pioneers, we will learn more about how to better treat glaucoma. We don't have the perfect MIGS yet, but in the end, we will get there."

The Next Phase: Sustainability

Dr. Ahmed expressed a similar view regarding future developments. He said that while it has been greatly satisfying to be involved in the early innovation process and see a large number of MIGS procedures "go mainstream," he had not fully anticipated the need for research on their cost-effectiveness and appropriate utilization.

Reimbursement challenges. "We are currently recognizing and building the right studies to look at quality-of-life issues, helping payers in the United States and Canada understand why MIGS should be funded a certain amount," Dr. Ahmed

A Comprehensive Ophthalmologist's Perspective on MIGS

Do MIGS have a place in the comprehensive ophthalmologist's armamentarium? Absolutely, according to Jeffrey Whitman, MD, a comprehensive ophthalmologist at the Key-Whitman Eye Center in Dallas.

"In our cataract patients with mild to moderate glaucoma, if we can get them off even one of their eyedrops by utilizing a MIGS approach, then we should offer this alternative," Dr. Whitman said. "One eyedrop may not seem like much, but over the course of a lifetime, that adds up to significant savings and greatly impacts the quality of life."

iStent, CyPass, and beyond. Dr. Whitman has been inserting iStents for the past 3 years and, within the last year, has begun using the CyPass. "In my early experience, I find the CyPass somewhat easier to insert, and I am obtaining much lower pressures than I could have imagined," he said.

He believes that the field will continue to advance, perhaps with combinations of MIGS or the addition of medications to stents for more potent treatment. (Glaukos and other companies are investigating these possibilities.)

MIGS myths limiting usage. Dr. Whitman observed that misconceptions about the effectiveness of MIGS procedures, the learning curve, and the time MIGS adds to cataract surgery are preventing many comprehensive ophthalmologists from adopting this approach.

"I encourage comprehensive ophthalmologists not to give up on MIGS but rather to reach out to other ophthalmologists and learn better techniques," Dr. Whitman said. "In terms of time, it makes an efficient cataract surgery take up to 50% longer, but I believe the benefits to the patient are well worth it."

Getting comfortable with MIGS. He added that getting accustomed to using a gonioscopic lens to view the angle and keeping the magnification at 9× (higher magnification results in less depth of field) will help comprehensive ophthalmologists become more comfortable with learning to do MIGS.

"My real take-home message to my colleagues is to get on the bandwagon with MIGS," Dr. Whitman said. "It doesn't add much time to cataract surgery, and it provides great benefit to your patient."

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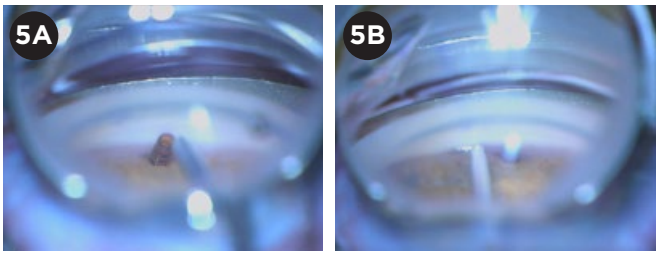
said. "We are looking at recovery, number of postsurgical visits, return to vision, and refractive changes—metrics that are of concern to entities funding these procedures."

Dr. Berdahl also pointed to reimbursement as one of the biggest challenges to widespread MIGS adoption. "MIGS is one of the only really impressive innovations in glaucoma in the last few decades. It will be tremendously sad if it withers on the vine," he said, for lack of reimbursement and resources to support innovation.



CYPASS + ISTENT. *(5A) CyPass is placed in the supraciliary space. (5B) iStent-L is placed, followed by an iStent-R facing in the opposite direction (not shown). The 2 iStents and a CyPass allow aqueous outflow through multiple pathways.*

1 Vinod K et al. *J Glaucoma.* 2017;26(8):687-693.
2 Ferguson TJ et al. *Clin Ophthalmol.* 2016;10:1767-1773.
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9 Lim KS et al. *Br J Ophthalmol.* 1998;82(9):1083-1089.

EXTRA **MORE ONLINE.** See this article at aao.org/eyenet for video resources, additional images, and more.

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Meet the Experts

Iqbal Ike K. Ahmed, MD Glaucoma specialist at the Prism Eye Institute in Mississauga, Ontario, Canada, assistant professor at the University of Toronto, and clinical professor at the University of Utah. *Financial disclosures: Abbott Medical Optics: C,L,S; Aerie Pharmaceuticals: C; Alcon: C,L,S; Allergan: C,L,S; ArcScan: C; Bausch + Lomb: C; Carl Zeiss Meditec: C,L,S; Centervue: C; Clarity: C,S; Envisia: C; Equinox: C; Eyelight: C; ForSight Labs: C; Glaukos: C,O,S; Gore: C; Iantech: C; InjectSense: C; InnFocus: C; Iridex: C; iStar: C; Ivantis: C,L,S; LayerBio: C; Leica: C; New World Medical: C,S; Oculus: C; Omega Ophthalmics: C; PolyActiva: C; Sanoculis: C; ScienceBased Health: C; SOLX: C; Stroma: C; Transcend Medical: C; TrueVision: C.*

John P. Berdahl, MD Glaucoma specialist at Vance Thompson Vision in Sioux Falls, S.D. *Financial disclosures: Abbott: C; Alcon: C,L; Allergan: C,L; Avedro: C; Bausch + Lomb: C; Calhoun Vision: C; Clarvista: C; Digisight: C,O; Envisia: C; Equinox: C,O; Glaukos: C,O; Imprimis: C,P; Ocular Surgical Data: C,O; Ocular Theraputix: C; Omega Ophthalmic: C,O; Vittamed: C.*

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Jeffrey Whitman, MD President and chief surgeon of the Key-Whitman Eye Center in Dallas. *Relevant financial disclosures: Glaukos: C,L; Ivantis: C.*

See disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.

*The views expressed are those of the individual and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. government. Any mention of products is for informational purposes only and should not be considered an endorsement.

INDICATION[1]

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

Please see Brief Summary of full Prescribing Information on the following pages.

HUMIRA®
adalimumab
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F1RST AND ONLY FDA-APPROVED ANTI-TNF FOR TREATING NON-INFECTIOUS (NI) UVEITIS*

For adult patients with non-infectious (NI) intermediate, posterior, and panuveitis[1]

NON-INFECTIOUS (NI) UVEITIS* CAN BE HARD TO CONTROL.

HUMIRA is proven to[1]:

- Provide steroid-sparing efficacy
- Prolong time to a combined measure of disease flare† and decrease of visual acuity

Visit www.HumiraPro.com/uveitis to learn more.

*Intermediate, posterior, and panuveitis.

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.

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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) plaque psoriasis (Ps), hidradenitis suppurativa (HS), and uveitis (UV) malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other

week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**

  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.

- **Malignancies**

  Counsel patients about the risk of malignancies while receiving HUMIRA.

- **Allergic Reactions**

  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.

- **Other Medical Conditions**

  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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Ref: 03-B374 Revised July 2016

64C-1865519 **MASTER**

64C-1875312

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Code-a-Palooza! Part 1: Could You Win Coding's Annual Game Show?

What's your favorite event at the annual meeting? For the past 5 years, one of my personal highlights has been Code-a-Palooza, an event like a game show. There are 2 teams that compete against one another *and* against the audience, which is supplied with a multiple-choice response system. This month and next, you can tackle some questions from the 2017 Code-a-Palooza.

Finger on the Buzzer!

Q1—when direct supervision is not needed. For Medicare Part B, which test does not require direct supervision (which is when a physician of the practice must be present on site)?

A. 76512 *Ophthalmic ultrasound, diagnostic; B-scan (with or without superimposed nonquantitative A-scan)*

B. 95930 *Visual evoked potential (VEP) testing central nervous system, checkerboard, or flash*

C. 92060 *Sensorimotor examination with multiple measurements of ocular deviation (e.g., restrictive or paretic muscle with diplopia) with interpretation and report (separate procedure)*

D. 92235 *Fluorescein angiography (includes multiframe imaging) with interpretation and report, unilateral or bilateral*

Q2—physician's John Hancock. Which statement is false with regard to a physician signature?

A. For paper charts, the signature log should be readily available.

B. If you have an electronic health record (EHR) system, the protocol for the EHR signature should be readily available.

C. Stamped signatures or physician signature/staff initials are still allowed if you have physician approval.

D. If the physician signature is missing, the physician may make an attestation statement.

E. If the physician signature is illegible, the payer can automatically request a recoupment without even auditing the documentation.

Q3—coding for butterfingers. Oops! As you were getting ready to inject a drug, you dropped the vial. Which of these statements is true?

A. Bill for the drug using a HCPCS code with modifier –52 *Reduced services.* When you fill out the CMS 1500 form, include the reason for reduced services in box 19, which is the box that is designated for "additional claim information."

B. Bill for the drug using a HCPCS code with modifier –59 *Distinct procedural service.* Include the reason in box 19 of the CMS 1500 form.

C. The lost drug is not reimbursable by the payer or patient. Contact the company rep to see if free drug can be provided.

D. Bill for the drug and double the units. Include the reason in box 19 of the CMS 1500 form.

Answers

1—when direct supervision is not needed. Answer: C is true. The sensori–motor exam has general supervision for Medicare Part B.

More to the story. Ophthalmic tests requiring direct supervision include:

- 76510 *Diagnostic A- and B-scan*
- 76511 *Quantitative A-scan*
- 76512 *B-scan*
- 76513 *Anterior segment ultrasound*
- 92235 *Fluorescein angiography (FA)*
- 92240 *Indocyanine green angiography (ICGA)*
- 92242 *FA and ICGA*
- 95930 *VEP*

For commercial payers who do not follow CMS rules, all tests require direct supervision.

2—physician's John Hancock. Answer: C is false. Stamped signatures or physician signature/staff initials are still allowed, provided that you have physician approval.

More to the story. According to CMS ICN 905634, stamped signatures are only permitted in the case of an author with a physical disability who can provide proof to a CMS contractor of inability to sign because of a disability.[1]

3—coding for butterfingers. Answer: C is true. The lost drug is not reimbursable by the payer or patient. Contact the company rep to see if free drug can be provided.

1 www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/Signature_Requirements_Fact_Sheet_ICN905364.pdf. Accessed Dec. 15, 2017.

BY **SUE VICCHRILLI, COT, OCS,** DIRECTOR OF CODING AND REIMBURSEMENT, AND **JENNY EDGAR, CPC, CPCO, OCS,** ACADEMY CODING SPECIALIST.

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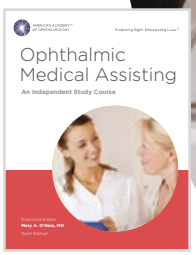

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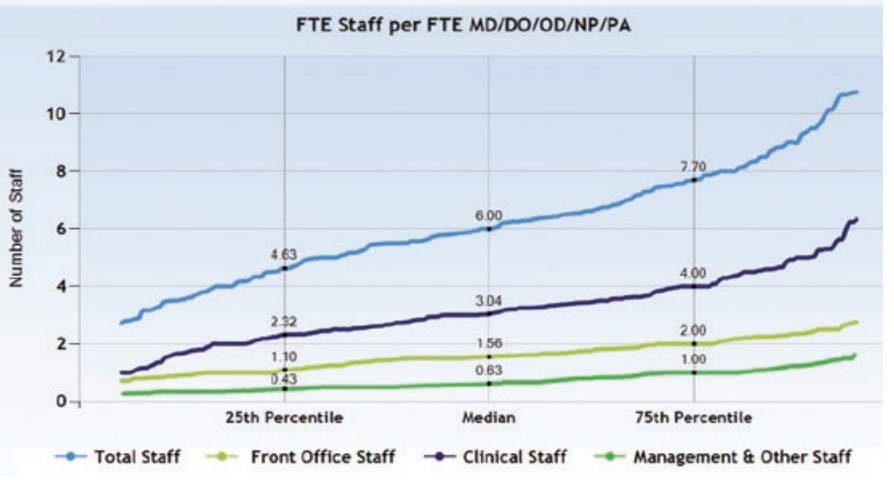
What Are the "Vital Signs" of Your Practice? See How You Rank on Dozens of Data Points

I could sense the frustration in the doctor's voice: "You've got to help us figure out what's wrong with our front-desk staff. My partners and I spend too much time standing around in the exam lane area waiting for patients to be processed at the front desk. I don't know why the receptionists can't get them registered quicker." We spoke a little longer, as I asked him questions and he provided the best answers he could. Before I left, I asked his office manager to send me 2 specific data points.

Benchmarking in action. A few days later we spoke again. I told him that the median number of patient encounters per full-time equivalent* receptionist was 2,800 per year. "Would you care to guess how many encounters your 2 receptionists are handling per year?" He didn't know, but because I had posed the question, he surmised that it was more than 2,800. "You're right," I confirmed, "Your staff handle about 3,600 encounters per year per full-time person, which is well above the 75th percentile. There may be some ways to streamline what they are doing so patients are processed faster, but the bottom line is this—your practice needs more help at your front desk!"

Having a benchmark for the number of encounters the front desk staff should be expected to handle per year allowed us to quickly identify one cause of the problem this doctor's practice was experiencing.



GET SOME PERSPECTIVE. *Compare your numbers on up to 72 indicators—such as staffing ratios (above)—with benchmarks based on similar practices.*

Know the Vital Signs of Practice Management

Benchmarks for ophthalmology practices are analogous to the vital signs that physicians measure in their patients before prescribing treatments. Suppose, for example, a patient presents with a blood pressure of 180/110. That reading would have limited value without a benchmark to compare it against; but an internist, aware that the benchmark is 120/80, would be concerned about the elevated pressure and would seek to identify and treat the underlying cause. In the same way, financial and patient flow benchmarks help you detect areas of your business that are not within normal limits.

AcadeMetrics benchmarks were developed specifically for ophthalmology practices. The Academy and AAOE provide a service—called AcadeMetrics—that enables you to compare your practice's financial and patient flow results with other, similar practices.

AcadeMetrics has 72 benchmarks. These include the following:

- **Overhead ratio**—judge how efficient your practice is in converting collections into cash for the owners.
- **Physician productivity ratios by subspecialty**—gauge whether your providers are seeing a typical number of patients and generating normal revenues.
- **Employee productivity ratios**—understand whether you have enough staff in various areas of the practice.
- **Accounts receivable ratios**—monitor your billing staff's effectiveness in collecting money owed to you.
- **Optical ratios**—analyze the profitability of your optical operations.

BY **DEREK PREECE, MBA,** PRINCIPAL AT BSM CONSULTING.

Many of the 72 benchmarks are unique to the AcadeMetrics survey and are not published elsewhere. Only data that are required to generate the benchmarks are collected, and practices that do not have an optical shop or a physician in a particular subspecialty can skip those fields.

AcadeMetrics—How to Start Benchmarking Your Practice

By participating in the AcadeMetrics survey, you'll be able to access detailed comparison reports that will help you to identify the specific strengths and weaknesses of your practice.

How it works. Each spring, ophthalmology practices start entering their data from the previous fiscal year. The resulting benchmarks and comparative reports will be available only to practices that complete at least 50% of the AcadeMetrics survey; the data won't be available for purchase by nonparticipants.

How to sign in. Sign in to the AcadeMetrics survey as follows:

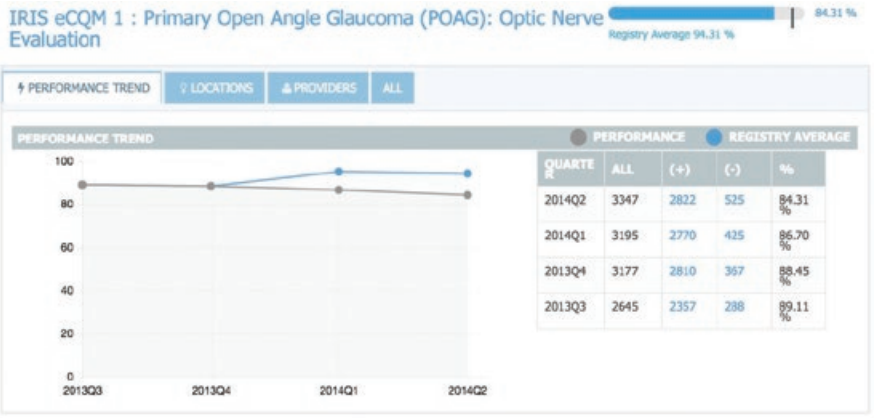
- If your practice is new to AcadeMetrics, register at https://academetrics.aao.org/academetrics_signup.aspx
- If your practice is a past participant in AcadeMetrics, you can use the same login that you used in previous years at https://academetrics.aao.org/

Your data are confidential. Your data will not be seen by other AcadeMetrics participants. Identifiers specific to your practice will be stripped from the final dataset, and the reporting tools will only display datasets that include a minimum of 10 items. (This minimum applies to both complete aggregated datasets and to any filtered dataset.)

Start using the benchmarks. You will be able to start comparing your performance against certain benchmarks as soon as you submit your data; other benchmarks will become available once enough participants complete the survey.

What does it cost? AcadeMetrics is free for Academy and AAOE members.

When can you get started? To find out when the AcadeMetrics benchmarking tool will open for collection of data from the 2017 fiscal year, see aao.org/academetrics.



YOU ALSO CAN USE THE IRIS REGISTRY FOR CLINICAL BENCHMARKING. *By benchmarking financial and patient flow performance, AcadeMetrics complements the IRIS Registry, which benchmarks clinical performance. If you have an electronic health record (EHR) system, you can integrate it with the IRIS Registry, which periodically extracts clinical data from your EHRs.*

For more information on the IRIS Registry, *including a list of EHR systems that have successfully been integrated with it, visit aao.org/iris-registry.*

Use AcadeMetrics Data to Identify Problems Early

The importance of knowing your key benchmarking figures was illustrated in a call that I received from a doctor several years ago. She phoned because the owners felt that they were making less-than-average income for ophthalmologists and thought they might need to cut some overhead expenses.

Benchmarking surfaces hidden problems. My analysis, using her practice's data and the AcadeMetrics benchmarking data, confirmed that their overhead ratio was too high, but it also showed that the main cause was that the physicians were generating collections well below the 25th percentile for their subspecialties.

An unidentified problem is an unsolved problem. Because no comparative benchmarking had been done in the practice, none of the physicians realized that they were bringing in much less revenue than their peers. And since they were unaware of the primary cause of their reduced income, they hadn't taken appropriate steps to address it. Consequently, over the previous years, their below-average revenue had prevented them from investing in the equipment needed to keep up to date, from ensuring their staff pay rates were competitive with the market, and from enjoying a more secure lifestyle.

Catch pernicious problems early. The situation at her practice reminded me of a quote that I had once read about high blood pressure: "The condition itself usually has no symptoms. You can have it for years without knowing it. During this time, though, high blood pressure can damage the heart, blood vessels, kidneys, and other parts of your body. Knowing your blood pressure numbers is important, even when you're feeling fine."

Likewise, knowing your AcadeMetrics benchmarking numbers can protect you from sustaining acute and immediate damage to your practice. Longer term, this knowledge can help prevent the silent impairment that could show up in your practice years later in unhealthy and sometimes irreversible ways.

For more information, visit aao.org/academetrics.

** To calculate how many full-time equivalent staff members you have, add up the total number of staff hours paid during the year and divide that by 2,080.*

Mr. Preece is a principal and executive consultant with BSM Consulting and assists Academy staff with the AcadeMetrics benchmarking survey.
Relevant financial disclosures: None.
For full financial disclosures, see this article at aao.org/eyenet.

Academy Notebook

NEWS ▫ TIPS ▫ RESOURCES

LEADERSHIP AND ADVOCACY. Renee C. Bovelle, MD, *LDP XX participant nominated by the Maryland Society of Eye Physicians and Surgeons, jots down notes during an LDP session.*

WHAT'S HAPPENING

Leadership Development Program Welcomes Its 20th Class

The Academy's Leadership Development Program (LDP) XIX held its graduation session during AAO 2017 in New Orleans. Concurrently, the Academy's 20th LDP (LDP XX) class met in an orientation session led by LDP director **Linda M. Tsai, MD.** Dr. Tsai joined the LDP XX class during a Jan. 12-14 meeting in San Francisco along with participants from the complementary leadership program of the Pan-American Association of Ophthalmology. In addition to visits to Academy headquarters to hear from **Keith D. Carter, MD,** Academy President, and **David W. Parke II, MD,** Academy CEO, the LDP participants attended 2½ days of interactive sessions on association management and leadership topics.

TAKE NOTICE

Your Academy's Year in Review

Academy leadership, staff, and countless volunteers work hard to provide you with the best member experience. Find out what the Academy achieved in the last year on all fronts, including advocacy, education, public service, and more. The 2017 Year in Review highlights some of the Academy's achievements:

- launched the David E.I. Pyott Glaucoma Education Center on the ONE Network
- introduced physician wellness resources on aao.org and at AAO 2017
- fought for ophthalmology's best interests in state and federal affairs

Read about these accomplishments and more at aao.org/yearinreview.

Submit Your Research to *Ophthalmology*

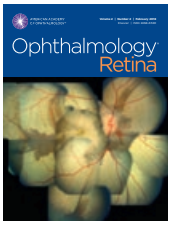
Ophthalmology, the Academy's flagship journal, publishes clinical and scientific research. Its unbiased peer-review process, advancement of innovation and discovery, and promotion of lifelong learning make it the leader in ophthalmic journals. With an impact factor of 8.2 and a print circulation of 27,000 subscribers, you can reach a larger audience than ever before.

To submit your research, visit www.evise.com/profile/#/ophtha/login.

ACADEMY STORE

The Latest Advances in Retina Delivered Monthly

Expanding to 12 issues per year in 2018, *Ophthalmology Retina* gives you access to the growing volume of important clinical advances in both medical and surgical retina. The journal will continue to feature high-impact articles, enabling you to stay on top of the latest developments in retina-focused medical therapy, imaging, surgery, technology, and science. Academy members receive a discounted rate of $299 for 12 issues.



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Register for Next Month's Ophthalmologists Business Summit

Join us on March 24 and 25 in Dallas for the Academy's first-ever Ophthalmologists Business Summit. Developed to help physician leaders overcome key business challenges, the summit addresses a need consistently raised by members for practice management training, especially relating to health care reform, reimbursement issues and electronic health records. Register by Feb. 28 to get a special rate and start planning for a prosperous future.

Register at aao.org/business-summit.

Order the 2018 Coding Update Webinar Recording

If you missed last month's important 2018 Ophthalmology Coding Update webinar, you can order the recording and get up-to-date on this year's coding changes and audit regulations. This 1-hour webinar covers significant revisions of diagnostic tests and procedures, deleted CPT and HCPCS codes, Medicare payment updates impacting ophthalmology, and more.

For more information, visit aao.org/store.

MEETING MATTERS

Join the Academy in Chicago for AAO 2018

Come to Chicago for AAO 2018 (Oct. 27-30) and Subspecialty Day (Oct. 26-27) to learn about game-changing research, techniques, and technologies. The meeting will be held in conjunction with the Pan-American Association of Ophthalmology, and it will take place at McCormick Place.

For more information about AAO 2018, visit aao.org/2018.

AAO 2018 Abstract Deadlines: Papers/Posters and Videos

To present at AAO 2018, you must submit abstracts online. The abstract submitter for papers/posters and videos opens March 8 and closes April 10.

Find abstract guidelines for videos and paper/posters at aao.org/presentercentral.

D.C. REPORT

Be Heard! Attend Mid-Year Forum 2018

The Mid-Year Forum is one of the Academy's most significant yearly meetings, bringing the ophthalmology community together to implement the highest quality of care for patients through politics, policy, and practice management. Mid-Year Forum 2018 takes place April 18-21 in Washington, D.C., and it is an ideal opportunity to directly advocate for your profession, learn about health care policy changes that will impact how you practice, and develop strategies to implement new patient care programs.

TAKING TO THE CAPITOL. *The Academy's 2018 President, Keith D. Carter, MD, with 2017 Advocacy Ambassador Program participants at Mid-Year Forum 2017.*

Congressional Advocacy Day—meet legislators at their place of business. On April 19, from 8:00 a.m. to 3:00 p.m., attend Academy-facilitated meetings with your members of Congress and their staff to advocate for your patients and the profession of ophthalmology. The Academy will brief you on talking points during dinner on April 18.

Politics. Policy. Practice management. On April 19 and 20, attend sessions on the changing role of the Veterans Health Administration; the scientific advancements and practice insights of the IRIS Registry; private equity and equity transfers; how to handle information overload; drugs in 2018 (access, pricing, and payment); the future of artificial intelligence in ophthalmology; and more.

Academy Council meeting. Beginning the afternoon of April 20 and continuing through the next day, unite with your colleagues from ophthalmic subspecialty and state societies to discuss issues facing our profession. The Academy Council meeting is also an opportunity to advise the Board of Trustees on what you view as the highest priorities for the Academy.

Register. Mid-Year Forum 2018 is open to all Academy members, and preregistration is available until April 3 at aao.org/myf_registration. The registration fee is $225 through March 6 and $325 as of March 7 and onsite, and the fee includes Mid-Year Forum materials and event-specific meals. There is an option to register to participate only in Congressional Advocacy Day for free.

AAO 2017 Archives

Visit Meeting Archives to access course handouts, find scientific poster abstracts, watch Videos on Demand, view syllabi from Subspecialty Day, download a list of companies that participated in the exhibition, and more. You can also find listings of Best Original Papers. Additional materials are posted as they become available.

To check out the archives, visit aao.org/aao-archives.

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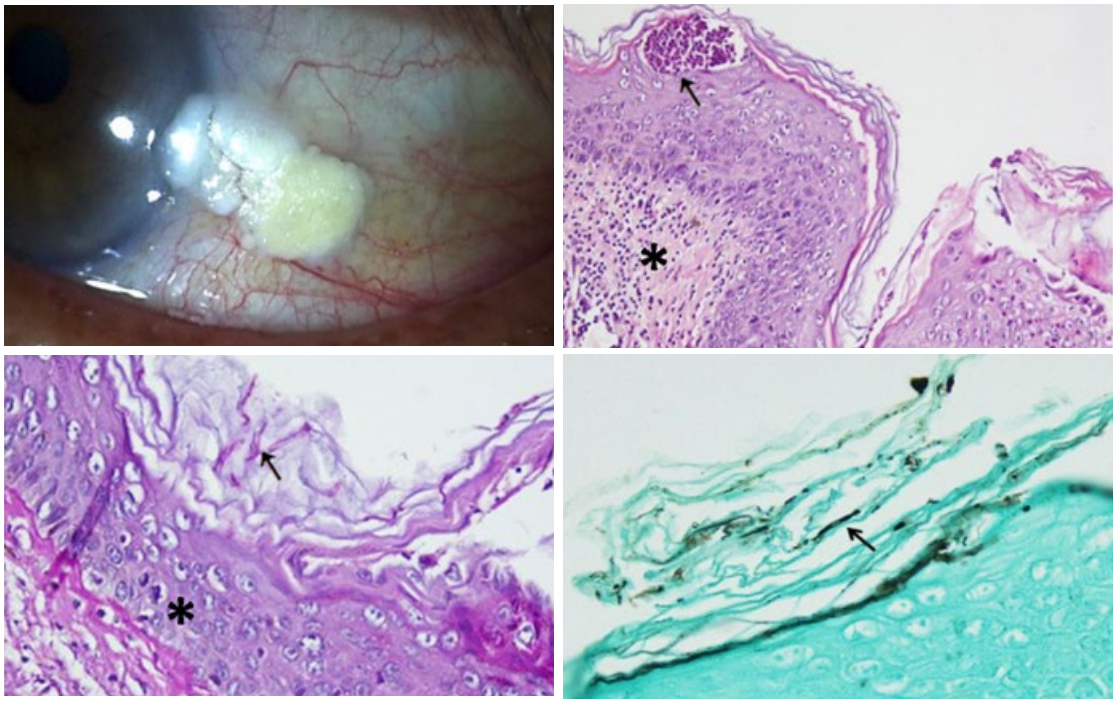
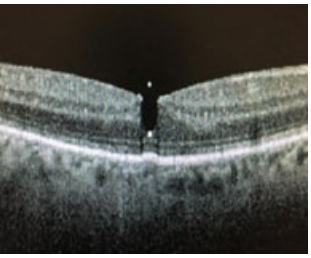


Anchal Thakur, MBBS, and Amit Gupta, MD, Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.*

LAST MONTH'S BLINK

PFO After Vitreoretinal Surgery



A 76-year-old man with a macula-on rhegmatogenous retinal detachment in his pseudophakic right eye underwent pars plana vitrectomy with perfluoropropane gas tamponade. Six weeks after surgery, his vision was 20/25 (back to baseline), the retina was attached, and the patient had no visual complaints. Spectral-domain optical coherence tomography (SD-OCT) imaging of the right macula demonstrated a hyporeflective (due to the scattering of light) oval-shaped vertically stretched area within the center of the fovea, with hyperreflective dots on the top and bottom tips of the oval area where light comes directly back to the OCT light detector. No retina material was detected overlying this bubble. This was consistent with retained preretinal perfluoro-n-octane (PFO) within the center of the foveal depression.

In addition, the OCT image of the retinal and choroidal material underneath the PFO bubble seems to be shifted upward, appearing closer to the light detector. This phenomenon is explained by light traveling more quickly through the PFO bubble compared to the surrounding aqueous. This happens because of the lower index of refraction of PFO (1.27) compared to that of humor/vitreous humor (1.336).

The PFO bubble appears to be vertically elongated in the portion within the retina, which is explained by the substance of the retina exerting a more horizontal compressive force compared to vertical. In the aqueous portion, the bubble takes a more rounded appearance, given the more even distribution of surface tension on this portion. The patient remained macula-on during the case, and given that the outer retina looks intact on OCT, it is unlikely that this bubble came from a subretinal location. It is possible that this preretinal PFO bubble got lodged into the foveal depression during a relatively high-pressure injection of PFO directed at the macula during the case.

Even though the bubble has no visible retinal roof (thin slice vertical and horizontal line scans show no overlying inner limiting membrane or epiretinal membrane material), it remains lodged within the central foveal depression at 12 weeks postoperatively. The patient remained asymptomatic, with no deficit on Amsler grid, and no change in refractive error or visual acuity at 7 months postoperatively.

WRITTEN BY **TAREK ALASIL, MD, OMAR SHAKIR, MD, MBA,** AND **PATRICK A COADY, MD, MBA.** SEE THIS ARTICLE AT AAO.ORG/EYENET FOR THEIR INSTITUTIONS.

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
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A Member of the Roche Group
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94080-4990

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(3) 2017

LUCENTIS 0.5 MG PREFILLED SYRINGE

EFFICACY DELIVERED

The efficacy and safety of LUCENTIS 0.5 mg studied in 7 pivotal trials,* available in a prefilled syringe.[1]

LUCENTIS®
RANIBIZUMAB INJECTION

INDICATIONS

LUCENTIS® (ranibizumab injection) 0.5 mg is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

Please see Brief Summary of LUCENTIS full Prescribing Information on next page.

*The following randomized, double-masked pivotal trials were conducted for the wet AMD, macular edema following RVO, and mCNV LUCENTIS indications: **wAMD:** *MARINA*—Phase III, multicenter, 2-year, sham injection–controlled study; primary end point at 1 year. *ANCHOR*—Phase III, multicenter, 2-year, active treatment–controlled study; primary end point at 1 year. *PIER*—Phase IIIb, 2-year, sham injection–controlled study; primary end point at 1 year. *HARBOR*—Phase III, multicenter, 2-year, active treatment–controlled dose-response study; primary end point at 1 year. **RVO:** *BRAVO*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. *CRUISE*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. **mCNV:** *RADIANCE*—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3.[2-8]

VEGF, vascular endothelial growth factor.

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