# RT Retina Today

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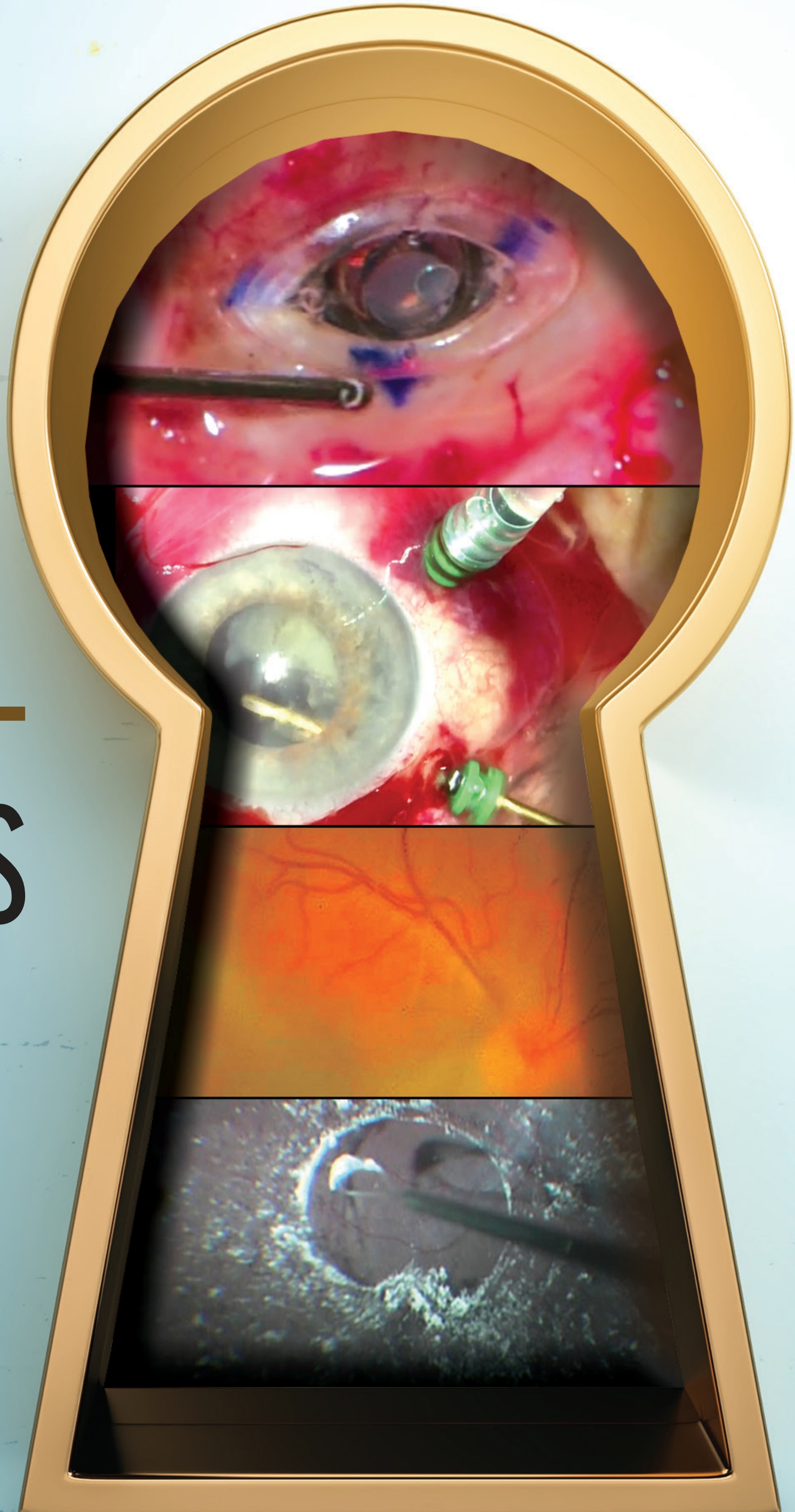
eyetube

# Techniques and Technologies



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## BUSINESS

**David Cox, President/Cofounder**
+1 484 581 1814; dcox@bmctoday.com

**Barbara Bandomir, Vice President, Operations**
+1 484 581 1810; bbandomir@bmctoday.com

**Tamara Bogetti, MBA**
**Executive Vice President/Group Publisher**
+1 714 878 0568; tbogetti@bmctoday.com

**Janet Burk, Vice President/Publisher**
+1 214 394 3551; jburk@bmctoday.com

**Gaynor Morrison, Vice President, Sales**
+1 484 581 1836; gaynor@bmctoday.com

**Ranna Jaraha, Director New Media**
+1 609 744 0111; rjaraha@bmctoday.com

**Brea Guggenheim, Manager Business Development**
+1 215 589 9656; bguggenheim@bmctoday.com

**Andy Lovre-Smith, Business Operations Manager**
+1 484 581 1850; alovre-smith@bmctoday.com

**Camela Pastorius, CMP, Vice President, Meetings & Events, Bryn Mawr Communications Group**
+1 484 581 1807; cpastorius@bmctoday.com

**David Levine, Executive Vice President, Digital & Custom Media**
+1 609 933 6799; dlevine@bmctoday.com

**Katherine Quraishi, Director, Digital Projects**
+1 484 581 1856; kquraishi@bmctoday.com

**Alvin Fu, Senior Director, Analytics & Technology**
+1 484 581 1888; afu@bmctoday.com

## EDITORIAL

**Rebecca Hepp, Editor-in-Chief**
+1 484 581 1880; rhepp@bmctoday.com

**Katie Herman, Associate Editor**
+1 484 581 1897; kherman@bmctoday.com

**Alexandra Brodin, Associate Editor**
abrodin@bmctoday.com

**Gillian McDermott, MA, Editor-in-Chief, Clinical Content, Anterior Segment**
+1 484 581 1812; gmcdermott@bmctoday.com

**Stephen Daily, Executive Editor, News**
+1 484 581 1871; sdaily@bmctoday.com

**Cara Deming, Director, Special Projects**
+1 484 581 1889; cdeming@bmctoday.com

## ART/PRODUCTION

**John Follo, Creative/Production Director**
+1 484 581 1811; jfollo@bmctoday.com

**Dominic Condo, Art/Production Director**
+1 484 581 1834; dcondo@bmctoday.com

**Joe Benincasa, Digital Art Director**
+1 484 581 1822; jbenincasa@bmctoday.com

**Rachel McHugh, Associate Art Director**
+1 484 581 1853; rmchugh@bmctoday.com

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# SCHOOL'S NEVER OUT

Do you remember how you felt at graduation, knowing that you were finally *done* with school? That sense of exhilaration didn't last long, did it? That's because the field of retina is evolving before our very eyes, and we never stop learning new techniques. Just like recent generations have learned to use all the new technologies that have come our way—computers, the internet, smartphones, virtual reality games, etc.—so too have retina specialists learned to integrate anti-VEGF therapy, small-gauge vitrectomy, OCT, and even gene therapy into our practices.

We are perpetual students. In fact, the way we care for our patients today is hardly recognizable compared with the treatment paradigms many of us learned in school. Even those of you who are newer to practice—1 to 5 years out of fellowship—are learning new surgical techniques and drug delivery approaches that were not taught during your time in the classroom.

In our last issue, we covered any and all therapies in the retina pipeline, which is always a fascinating exploration of what will likely be our future. This issue, we roll up our sleeves and tackle what's changing our practices *now*. Thanks to the hard work of our colleagues and industry partners, we have several new tools at our disposal.

This issue is all about solving today's retina care problems: postoperative complications, treatment burden, timely diagnoses, you name it. But it's not always easy to incorporate new technologies and therapeutics into our practices—and boy, are some of the new options disruptive (in a good way, of course). So here we are giving you practical tips to help you feel more comfortable integrating these new tools and techniques into your practice.

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) is a sea change in our field and offers a surgical option in the management of wet AMD, particularly for those patients with high treatment burden. To help all of us add this new surgical approach into our clinical armamentarium, we asked Dante J. Pieramici, MD; Nika Bagheri, MD; and Austin Couvillion, BA, to share some of the tips and tricks they have learned while implanting the device during the clinical trials. Their 10 surgical pearls can augment your training to ensure you hit the ground running with the first long-duration anti-VEGF therapy.

Other new concepts sending us back to the classroom, so to speak, include new delivery targets, such as subretinal gene therapy and suprachoroidal injections. Those are covered by Aaron Nagiel, MD, PhD, whose article is peppered with tips as he explains the benefits and challenges of these new approaches. Theodore Leng, MD, and Kapil Mishra, MD, also touch on the first therapy delivered to the suprachoroidal space to be FDA-approved, Xipere (triamcinolone acetonide injectable suspension, Bausch + Lomb) and where it fits into our list of long-duration steroid options.

As for new technologies, we have a few that might have us cracking open a training manual or two. Small-gauge vitrectomy is making surgical intervention a possibility for several conditions that normally wouldn't send a patient to the OR, such as for visually significant opacities, according to Matthew A. Cunningham, MD, and Jaya B. Kumar, MD. They discuss how proper patient selection is the key to this otherwise straightforward procedure.

Another new tool shaking things up in the OR is hypersonic vitrectomy. While still in early-stage development, it is FDA-approved and just might change how some of us perform vitrectomy in the future. The open port and ultrasonic energy are completely different from what we are used to, so if you are thinking of implementing this tool, be sure to read this issue's article by Samir N. Patel, MD; Asael Papour, PhD; and Michael A. Klufas, MD.

And last but certainly not least, we gathered experts in the field to discuss one of the most challenging aspects of vitreoretinal surgery: the potential for postoperative vitreoretinopathy. Despite the leaps and bounds we have made in other areas of patient care, this remains a significant concern, and one we have yet to address well medically or surgically. Of course, a new study investigating intravitreal methotrexate (Aldeyra Therapeutics) might change all that, but until then, we share some of the preoperative planning and surgical techniques that have helped quell this complication in our clinics.

We are all in this together, and this year, we all have some learning to do. ■

**ALLEN C. HO, MD**
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**YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection**
**Initial U.S. Approval: 1963**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

**1. INDICATIONS AND USAGE.** YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

**4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections.** YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

**5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects.** Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

**6. ADVERSE REACTIONS. 6.1. Clinical Studies 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 another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

**Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients**

| Ocular | | |
|---|---|---|
| **ADVERSE REACTIONS** | **YUTIQ (N=226 Eyes) n (%)** | **Sham Injection (N=94 Eyes) n (%)** |
| Cataract[1] | 63/113 (56%) | 13/56 (23%) |
| Visual Acuity Reduced | 33 ( 15%) | 11 (12%) |
| Macular Edema | 25 ( 11%) | 33 (35%) |
| Uveitis | 22 ( 10%) | 33 (35%) |
| Conjunctival Hemorrhage | 17 ( 8%) | 5 ( 5%) |
| Eye Pain | 17 ( 8%) | 12 (13%) |
| Hypotony Of Eye | 16 ( 7%) | 1 ( 1%) |
| Anterior Chamber Inflammation | 12 ( 5%) | 6 ( 6%) |
| Dry Eye | 10 ( 4%) | 3 ( 3%) |
| Vitreous Opacities | 9 ( 4%) | 8 ( 9%) |
| Conjunctivitis | 9 ( 4%) | 5 ( 5%) |
| Posterior Capsule Opacification | 8 ( 4%) | 3 ( 3%) |
| Ocular Hyperemia | 8 ( 4%) | 7 ( 7%) |
| Vitreous Haze | 7 ( 3%) | 4 ( 4%) |
| Foreign Body Sensation In Eyes | 7 ( 3%) | 2 ( 2%) |
| Vitritis | 6 ( 3%) | 8 ( 9%) |
| Vitreous Floaters | 6 ( 3%) | 5 ( 5%) |
| Eye Pruritus | 6 ( 3%) | 5 ( 5%) |
| Conjunctival Hyperemia | 5 ( 2%) | 2 ( 2%) |
| Ocular Discomfort | 5 ( 2%) | 1 ( 1%) |
| Macular Fibrosis | 5 ( 2%) | 2 ( 2%) |
| Glaucoma | 4 ( 2%) | 1 ( 1%) |
| Photopsia | 4 ( 2%) | 2 ( 2%) |
| Vitreous Hemorrhage | 4 ( 2%) | 0 |
| Iridocyclitis | 3 ( 1%) | 7 ( 7%) |
| Eye Inflammation | 3 ( 1%) | 2 ( 2%) |
| Choroiditis | 3 ( 1%) | 1 ( 1%) |
| Eye Irritation | 3 ( 1%) | 1 ( 1%) |
| Visual Field Defect | 3 ( 1%) | 0 |
| Lacrimation Increased | 3 ( 1%) | 0 |
| Non-ocular | | |
| **ADVERSE REACTIONS** | **YUTIQ (N=214 Patients) n (%)** | **Sham Injection (N=94 Patients) n (%)** |
| Nasopharyngitis | 10 ( 5%) | 5 ( 5%) |
| Hypertension | 6 ( 3%) | 1 ( 1%) |
| Arthralgia | 5 ( 2%) | 1 ( 1%) |

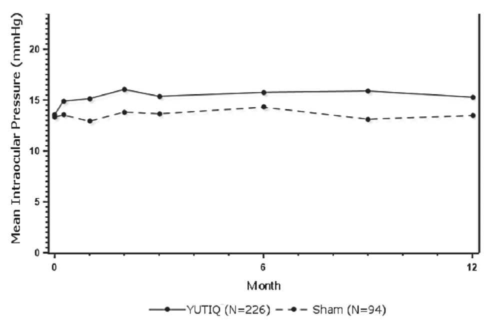
(continued)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

**Table 2: Summary of Elevated IOP Related Adverse Reactions**

| **ADVERSE REACTIONS** | **YUTIQ (N=226 Eyes) n (%)** | **Sham (N=94 Eyes) n (%)** |
|---|---|---|
| IOP elevation ≥ 10 mmHg from Baseline | 50 (22%) | 11 (12%) |
| IOP elevation > 30 mmHg | 28 (12%) | 3 (3%) |
| Any IOP-lowering medication | 98 (43%) | 39 (41%) |
| Any surgical intervention for elevated IOP | 5 (2%) | 2 (2%) |

**Figure 1: Mean IOP During the Studies**




**8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy.** Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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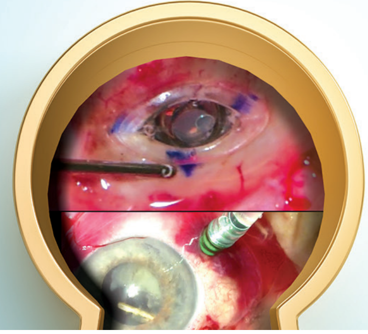

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# LHON THERAPIES MOVE THROUGH CLINICAL TRIALS

Two companies, GenSight Biologics and Mitotech, are investigating treatment options for Leber hereditary optic neuropathy (LHON) and have reported positive updates for their drug candidates.

## Gene Therapy

Intravitreal injection with the gene therapy lenadogene nolparvovec (Lumevoq, GenSight Biologics) remained safe and effective at 2 years of follow-up in the REFLECT clinical trial, according to a recent company press release.[1]

REFLECT is a randomized, double-masked, placebo-controlled phase 3 trial designed to evaluate lenadogene nolparvovec for the treatment of LHON associated with mutation in the *ND4* mitochondrial gene, the most severe form of the disease. The study involved 98 participants, all of whom received at least one injection of the study drug in an affected eye; 48 were randomized to receive a second injection of lenadogene nolparvovec in their other eye, while the remaining 50 received a placebo.

At the 2-year follow-up, eyes treated with the gene therapy showed significant sustained improvement from baseline BCVA, with greater efficacy seen in patients treated bilaterally. Placebo-treated eyes did not show statistically significant improvement. The data also revealed a promising safety profile for bilateral treatment. The most common adverse event was mild intraocular inflammation, and there were no serious systemic or ocular adverse events.

GenSight is pursuing regulatory approval for treatment of LHON, and individuals treated in the REFLECT trial have been invited to participate in a 5-year follow-up study of lenadogene nolparvovec.

## Topical Therapy

The FDA has granted orphan drug designation for the topical cardiolipin peroxidation inhibitor Visomitin (Mitotech SA) for the treatment of LHON.[2] The drug—already in phase 3 trials for dry eye disease (DED) and under investigation for glaucoma, uveitis, and dry AMD—demonstrated consistent improvement in visual acuity in patients in a 3-year open-label phase 2a study conducted outside of the United States. Visual improvement was noted in patients with various underlying mutations, such as *G11778A*, for whom the chances of improvement are typically low.[2]

The company is planning to start a phase 2 study of the cardiolipin peroxidation inhibitor in patients with LHON in 2022 in collaboration with the Doheny Eye Institute at the University of California Los Angeles. The planned study aims to develop the drug candidate as a convenient and potentially high-impact treatment for LHON. ■

1. GenSight biologics confirms sustained efficacy and safety of bilateral lumevoq injections at 2-year follow-up of REFLECT phase 3 trial [press release]. December 14, 2021. Accessed January 3, 2022. eyewire.news/news/gensight-biologics-confirms-sustained-efficacy-and-safety-of-bilateral-lumevoq-injections-at-2-year-follow-up-of-reflect-phase-3-trial
2. Mitotech SA. Mitotech granted orphan drug designation by FDA for Visomitin in LHON [press release]. December 15, 2021. Accessed January 3, 2022. www.mitotechpharma.com/news/mitotech-granted-orphan-drug-designation-by-fda-for-visomitin-in-lhon

# TWO TREATMENT STRATEGIES FOR L-ORD SHOW PROMISE

Researchers from the National Eye Institute have found that two potential treatments for late-onset retinal degeneration (L-ORD)—gene therapy and the diabetes drug metformin—successfully prevented signs of the disease in vitro.[1] L-ORD is a heritable blinding disease that causes a mutation in the gene that encodes the CTRP5 protein, leading to abnormal blood vessel growth and deposits of apolipoprotein E, which is involved in the metabolism of fat in the retina. As the disease progresses, retinal pigment epithelium (RPE) cells begin to degenerate, culminating in loss of vision.

Using patient-derived RPE models developed from induced pluripotent stem cells of four siblings (two with L-ORD and two who were unaffected for comparison) the researchers identified a link between the presence of the mutation and chronic activation of AMP-activated protein kinase (AMPK), which helps regulate homeostasis and fat


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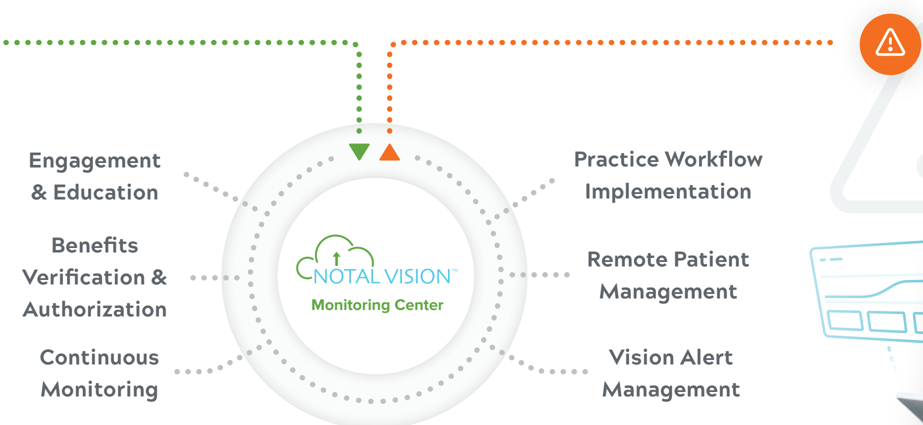




**References: 1.** Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

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SM-125.2

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metabolism. Moreover, they found that inhibition of AMPK led to fewer apolipoprotein E deposits and less abnormal secretion of VEGF.[1]

Next, the researchers used the models to test two potential treatment strategies: gene therapy to encourage production of the normal gene for CTRP5 and use of metformin, which appears to help regulate AMPK activity. Both methods effectively prevented signs of L-ORD in the RPE models.[1]

Plans for a clinical trial to test the diabetes drug in patients with L-ORD are currently underway.

1. National Institutes of Health. NIH study traces molecular link from gene to late-onset retinal degeneration [press release]. December 9, 2021. Accessed January 3, 2022. www.nei.nih.gov/about/news-and-events/news/nih-study-traces-molecular-link-gene-late-onset-retinal-degeneration

## POSITIVE RESULTS OF PHASE 3 STUDY IN DIABETIC MACULAR EDEMA

Novartis announced the year 2 results of their phase 3 KESTREL study assessing the safety and efficacy of 6 mg brolucizumab (Beovu) in patients with diabetic macular edema (DME). Results are consisted with those seen at year 1 with patients maintaining BCVA and sustained reductions in central subfield thickness. At year 2, fewer patients treated with brolucizumab had intraocular fluid and/or subretinal fluid compared with those treated with aflibercept (Eylea, Regeneron).

However, rates of intraocular inflammation continued to be higher for the treatment group compared with aflibercept: 4.2% for 6 mg brolucizumab, 5.3% for 3 mg brolucizumab, and 1.1% for aflibercept. Most cases were manageable and resolved without clinical complications.[1] Rates of retinal vascular occlusion were 1.6% for both the 6 mg and 3 mg brolucizumab groups versus 0.5% for aflibercept.[1] Four new retinal vascular occlusion events were reported (two in the 6 mg group, one in the 3 mg group, and one in the aflibercept group), however, none were associated with intraocular inflammation or retinal vasculitis. There were no vascular events reported.

1. Novartis announces positive results from year two of the phase III trial of Beovu in diabetic macular edema [press release]. Novartis. December 9, 2021. Accessed January 5, 2022. www.novartis.com/news/media-releases/novartis-announces-positive-results-from-year-two-phase-iii-trial-beovu-diabetic-macular-edema

## FDA REGISTERS FIRST SMARTPHONE-BASED PRODUCT FOR RETINAL HEALTH TESTING

SmartERG (Evoq Technologies), a smartphone-based biosensor technology for dark adaptation impairment testing for retinal diseases, was registered with the FDA as a Class I medical device. This device provides the option for in-office or at-home testing.

SmartERG uses controlled flashes of light emitted from a smartphone to evoke an electrical-physiological response from the retina, according to a company press release. The head-mounted biosensor sends data to the smartphone app via a Bluetooth connection. The SmartERG platform offers a new delivery method for ophthalmic patient-to-provider care, according to Evoq.

Evoq is seeking licensing and partnership opportunities with pharmaceutical, medical device, and clinical research organizations. The company plans on conducting clinical evaluations of the SmartERG platform and specialty stimulators for submission as Class II medical devices with the FDA this year.

1. Evoq Technologies announces launch of first smartphone-based product for retinal health testing [press release]. November 22, 2021. Accessed January 5, 2022. eyewire.news/news/evoq-technologies-llc-announces-launch-of-first-smartphone-based-product-for-retinal-health-testing

## STUDY QUESTIONS VISUAL BENEFIT OF TREATMENT WITH LUXTURNA

A multicenter, retrospective study of the effects of treatment with voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) showed that patients treated with the gene therapy between January 2018 and May 2020 did not experience persistent changes in vision.

Nonetheless, the study authors found a trend toward improvement for children that reached statistical significance for some, but not all, time points.

Mean follow-up was 10 months (range 1 week to 18.5 months). Among the 41 patients included (16 adults and 25 children; 77 total eyes), 29% of pediatric eyes and 12% of adult eyes improved ≥ 2 lines ($P = .15$) at last follow-up.[1] Central foveal thickness decreased in both groups, with no significant difference between adults and children, and the fovea was detached in 62 (81%) of eyes. Of 54 eyes with gradable OCT images, the inner segment–outer segment junction remained unchanged in 91%.[1]

According to a survey that reached 32 patients (78%), improvements in day, night, and color vision were reported by 23 (72%), 22 (69%), and 18 (56%) patients, respectively.[1]

Voretigene neparvovec-rzyl was approved by the FDA in December 2017 for the treatment of patients with *RPE65* mutation–associated retinal dystrophy. The results indicate that treatment with the gene therapy did not lead to persistent, statistically significant visual improvement.

The authors note that the study was limited due to the large variability in follow-up time and that further research is needed to determine the relevance of these preliminary findings.[1] ■

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RT Retina Today

# ONE TO Watch

## BASIL K. WILLIAMS JR, MD

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### Please share with us your background.

I was born in St. George's, Grenada, and grew up in the South Bronx, New York City. My dad is a Pentecostal minister, so I spent a significant amount of time in church or playing basketball. In the summer, my friends and I would play from sunup to sundown. In the winter, we shoveled snow off the court and played until our fingers became immobile.

### When did you first know that you wanted to become a vitreoretinal surgeon?

My family maintains that they knew I would be an ophthalmologist ever since I won my second-grade science fair with my model eye. While that was definitely a childhood highlight, I think the impact of wearing coke-bottle glasses or goggles while playing sports had a much larger impact.

After graduating from college, I worked as a technician in a retina practice under Peter Liggett, MD, who also treated patients with uveal melanoma. His caring nature and bedside manner made a lasting impression on me—I continue to use some of his phrasing and approaches to this day. In particular, there was a young woman with a large melanoma that ultimately required enucleation, and I was captivated by how he navigated that conversation and instilled confidence in her about her future. I knew then that I was going to be a retina specialist and ocular oncologist.

### Who are your mentors?

The phrase "it takes a village to raise a child" is most definitely true in my situation. Dr. Liggett helped me begin my path to ophthalmology and connected me with William F. Mieler, MD, who was Chairman of the Department of Ophthalmology at the University of Chicago at the time. The Chicago Medical School did not have an ophthalmology department, so Dr. Mieler was kind enough to let me spearhead a project as a first-year medical student.

I spent a summer doing research with Timothy G. Murray, MD, MBA, at the Bascom Palmer Eye Institute in Miami, an opportunity that I believe changed my career trajectory. That summer, I worked closely with Amy C. Schefler, MD, who has remained a constant source of advice, serving as a sounding board for my job choices and career aspirations. Also, Audina M. Berrocal, MD, has taught me as much about life outside of work as she has about retina and surgery.

### Describe your current position.

I work at the University of Cincinnati in adult and pediatric ocular oncology and interact with medical oncology, radiation oncology, and pediatric oncology to comanage patients. At Cincinnati Children's Hospital Medical Center, I evaluate pediatric patients and collaborate with pediatric neurosurgeons when intraarterial chemotherapy is indicated. Lastly, I also practice surgical retina at the Cincinnati Eye Institute. The broad range of practice settings, pathologies, and patients makes every day a bit different.

### What has been the most memorable experience of your career thus far?

I started seeing a boy with retinoblastoma. He had already undergone an enucleation in one eye and was battling recurrent disease in his remaining eye. After 3 years of trying every treatment available, including an experimental therapy in a clinical trial, he achieved remission but continued treatment for radiation retinopathy and severe dry eye from a radiation-induced neurotrophic cornea. While receiving regular anti-VEGF injections with an intensive topical lubrication regimen, he maintained a positive attitude. Every month, he told me of all the places in New York City he wanted to visit, knowing I grew up there.

About 6 months ago, his family took him to New York, and he had the biggest smile and a million stories for me on his next follow-up. This interaction forced me to step back and appreciate the amazing opportunity I have to make a difference despite the struggles that happen along the way.

### What advice do you have for individuals who are choosing their career paths?

Identifying your long-term career path after finishing fellowship can be very difficult as opportunities and interests change over time. Keeping in touch with your mentors can be an invaluable aid in navigating those challenges. ■

**BASIL K. WILLIAMS JR, MD**

- Assistant Professor of Ophthalmology, Director of Ocular Oncology, University of Cincinnati, Cincinnati, Ohio
- Vitreoretinal Surgeon, Cincinnati Eye Institute, Cincinnati, Ohio
- basilkwilliams@gmail.com
- Financial disclosure: Consultant (Allergan, Castle Biosciences, Genentech)

# SLO-BASED WIDEFIELD IMAGING: AN ATLAS OF RETINAL DETACHMENTS

This new tool captures peripheral pathology, augmenting standard examinations.

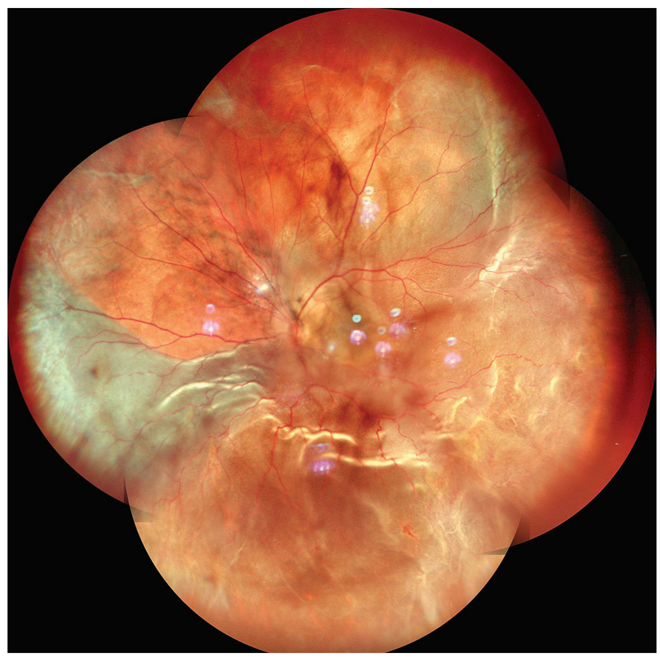
**BY MANISH NAGPAL, MS, FRCS, FASRS; NAVNEET MEHROTRA, MBBS, DNB, FRF; AKANSHA SHARMA, MBBS, MS; NIVESH GUPTA, MBBS, MS; AND ABHISHEK VERMA, MBBS, DO**

Various ocular diseases present with findings in the retinal periphery, making widefield imaging a useful tool for diagnosis, monitoring response to therapy, and telemedicine. Widefield fundus imaging does not replace dilated ophthalmoscopy, but it is often an important adjunct to escalate the clinical examination. Vigilant clinical examination of the peripheral retina with scleral indentation is crucial for clinical decision making, and auxiliary testing with scanning laser ophthalmoscopy (SLO)-based widefield imaging can help to document findings.[1] The case series presented here demonstrates the utility of SLO-based imaging for patients presenting with signs and symptoms of rhegmatogenous retinal detachment (RD).

We captured widefield fundus photographs of six patients who presented with RD. The patients underwent refraction, IOP assessment, slit-lamp examination, and dilated indirect ophthalmoscopy by a specialist. The SLO had a widefield (163° measured from the center of the eye) lens attachment available. The device scans the retina through a confocal optical setup with a small coaxially placed pinhole that lets light in from the focal planes, while blocking backscattered and out-of-focus light.

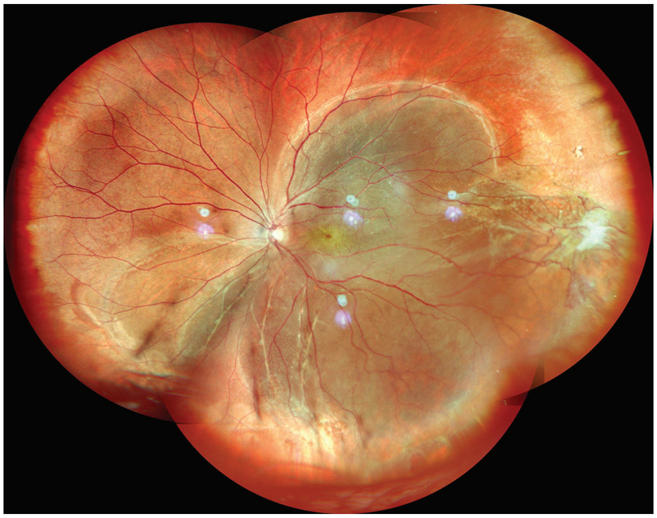
## CASE NO. 1

A 36-year-old male presented with loss of vision in the left eye for 1 month and a VA of 6/60. He was diagnosed with a macula-off RD in the left eye. Widefield fundus imaging of the left eye revealed the RD extending between 2 and 10 clock hours with multiple holes seen inferiorly between the 5 and 6 clock hours. He underwent bimanual vitrectomy with gas. Postoperatively, his VA was 6/24 OS.



## CASE NO. 2

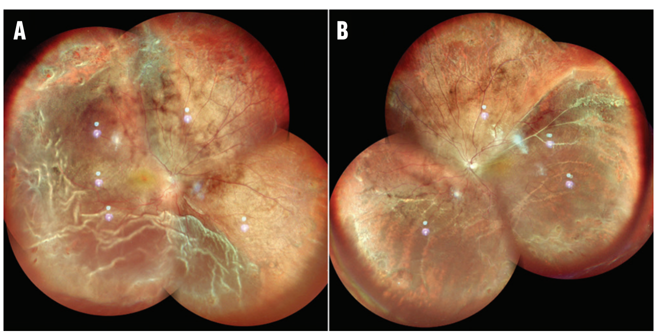
A 24-year-old male presented with decreased vision in the left eye for 2 years and VA of counting fingers at 3 m. He gave a history of RD surgery performed elsewhere for the same complaint. SLO-based widefield fundus photography of the left eye showed an RD extending from 3 to 8 clock hours with proliferative vitreoretinopathy and a demarcation line inferonasally. Several holes were seen inferiorly between the 4 and 6 clock hours. We performed bimanual vitrectomy on



the left eye with silicone oil infusion. He reported a VA of 6/36 OS postoperatively.

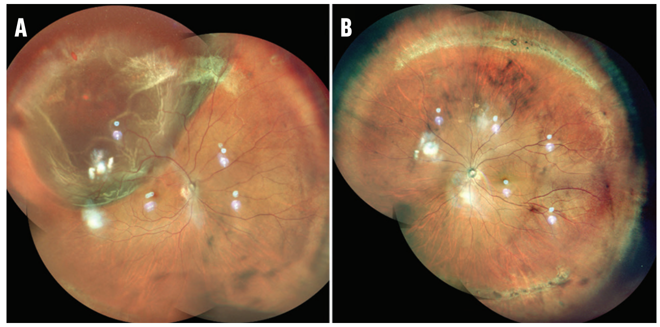
## CASE NO. 3

A 22-year-old male presented with loss of vision in both eyes for 1 month. He had a VA of 6/60 OU. On widefield fundus photography, we noted a subtotal macula-off RD in his right eye extending between the 5 and 12 clock hours (A). There were multiple small holes extending between the 8 and 11 clock hours. He also had an RD in the left eye extending between the 2 and 8 clock hours with multiple holes inferiorly and temporally between the same clock hours (B). We recommended a scleral buckle with bimanual vitrectomy for both eyes, which was successful.




## CASE NO. 4

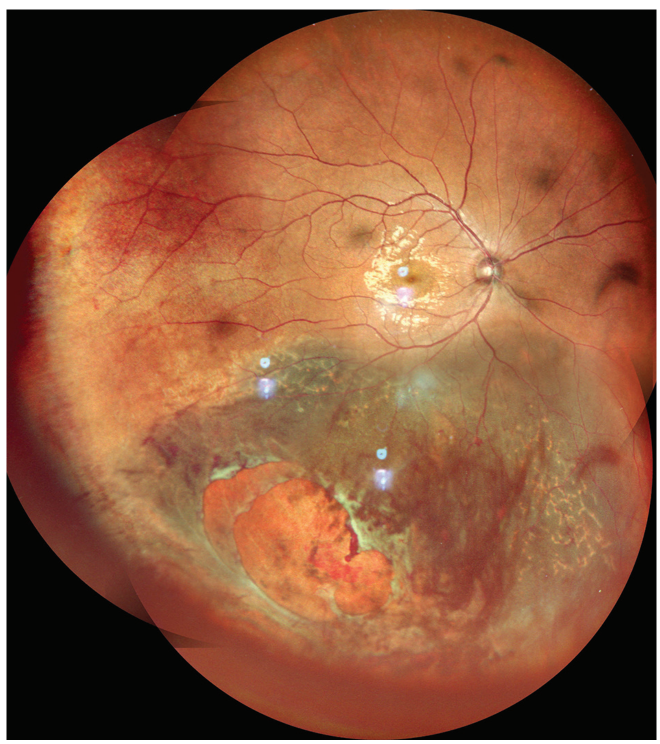
A 44-year-old male presented with diminished vision in the right eye for 6 days. His VA was 6/6 OU. Widefield fundus photography showed an RD in the right eye superiorly extending between the 9 and 12 clock hours with two holes superotemporally at the 10 clock hour with lattice degeneration inferotemporally (A). Imaging showed lattice degeneration in the left eye with multiple holes present superiorly




between the 11 and 2 clock hours and inferiorly pigmented lattice between the 5 and 7 clock hours (B). The patient underwent bimanual vitrectomy with gas in the right eye and prophylactic laser treatment in the left eye. Postoperatively he reported a VA of 6/6 OD.

## CASE NO. 5

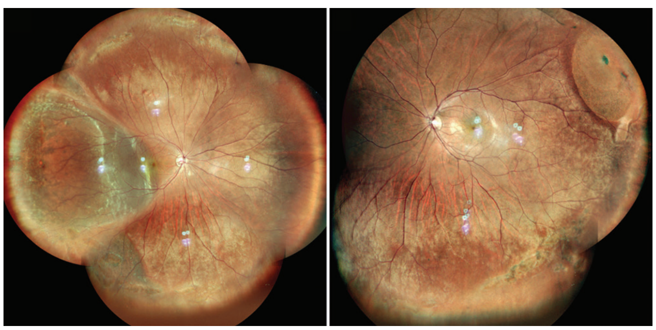
A 29-year-old male presented with loss of vision in the right eye 10 days, after being hit in the eye with a tennis ball. He reported a VA of 6/6 OD and gave a history of laser treatment for a retinal tear in the right eye, performed at another clinic. SLO-based widefield imaging revealed an RD extending between the 4 and 8 clock hours with a large tear inferiorly extending between the 6 and 8 clock hours that had organized vitreous hemorrhage around it. He underwent bimanual vitrectomy with gas in the right eye and reported a postoperative VA of 6/6 OD.



# TO EFFICIENTLY IDENTIFY RETINAL DETACHMENTS USING ARTIFICIAL INTELLIGENCE, THE FIRST STEP IS TO OBTAIN FUNDUS IMAGES COVERING THE PERIPHERAL RETINA—MADE POSSIBLE WITH RECENT TECHNOLOGICAL ADVANCES, SUCH AS SLO-BASED IMAGING.

## CASE NO. 6

A 31-year-old male presented with diminished vision in the right eye for 1 week. His VA was 6/36 OD and 6/6 OS. Widefield fundus photography revealed a macula-off RD extending between the 7 and 10 clock hours. Multiple holes with lattice degeneration were noted at the 9 clock hour. Multiple lattices were also seen at the 11, 1, 2, and 7 clock hours. In his left eye, a schitic area was found between the 1 and 2 clock hours, and inferior lattice was seen between the 4 and 6 clock hours. He was treated with bimanual vitrectomy with silicone oil infusion for his right eye and a prophylactic laser 1 month later for his left eye. He reported a postoperative VA of 6/18 OD.



## DISCUSSION

Widefield images are defined as single-capture images centered on the fovea that capture retinal anatomic features beyond the posterior pole, but posterior to the vortex vein ampulla, in all four quadrants.[2] To efficiently identify RD using artificial intelligence, the first step is to obtain fundus images covering the peripheral retina—made possible with recent technological advances, such as SLO-based imaging. Of course, dilated fundus examination by a clinician with the help of an indirect ophthalmoscope remains the standard of care for RD diagnosis.

In our study, we performed a complete dilated indirect ophthalmoscopic examination of the patients before capturing fundus photography. We found that the SLO-based fundus images were on par with the clinical findings obtained through the dilated fundus examination by the specialist.

Our results show that SLO-based widefield imaging can provide the necessary details to help clinicians effectively diagnose RD.

This system can be used to detect RDs as a part of ophthalmic health in busy hospitals lacking access to ophthalmic specialists. It can also help to reveal peripheral RDs in patients who cannot endure a dilated fundus examination. Widefield images such as those presented in this article may also alleviate the burden of documenting myriad peripheral lesions. Moreover, they add an objective aspect to the documentation, which can augment subjective perceptions in charting. ■

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**NIVESH GUPTA, MBBS, MS**
- Vitreoretinal Fellow, Retina Foundation, Ahmedabad, India
- gnivesh1@gmail.com
- Financial disclosure: None

**NAVNEET MEHROTRA, MBBS, DNB, FRF**
- Vitreoretinal Consultant, Retina Foundation, Ahmedabad, India
- navneetmeh@yahoo.com
- Financial disclosure: None

**MANISH NAGPAL, MS, FRCS, FASRS**
- Senior Consultant, Retina and Vitreous Services, Retina Foundation, Ahmedabad, India
- Editorial Advisory Board Member, *Retina Today*
- drmanishnagpal@yahoo.com
- Financial disclosure: Consultant (Nidek)

**AKANSHA SHARMA, MBBS, MS**
- Vitreoretinal Fellow, Retina Foundation, Ahmedabad, India
- akanshasharma1993@gmail.com
- Financial disclosure: None

**ABHISHEK VERMA, MBBS, DO**
- Vitreoretinal Fellow, Retina Foundation, Ahmedabad, India
- abhishekssverma@gmail.com
- Financial disclosure: None

# RRD REPAIR INTEGRITY: VITRECTOMY VERSUS PNEUMATIC RETINOPEXY


Are different surgical procedures associated with a difference in the integrity of retinal reattachment?

BY RAJEEV H. MUNI, MD, MSC, FRCSC, AND INGRID U. SCOTT, MD, MPH

As vitreoretinal surgeons, one of the most basic techniques we learn is reattaching the retina following rhegmatogenous retinal detachment (RRD). Many vitreoretinal surgeons were taught by mentors who were trained to favor the use of a scleral buckle (SB) for RRD repair. However, these mentors have also witnessed a tremendous evolution in vitreoretinal surgery over the past 10 to 15 years, with small-gauge pars plana vitrectomy (PPV) becoming an essential procedure for many conditions such as diabetic vitreous hemorrhage, tractional retinal detachment, macular hole repair, and epiretinal membrane removal.

Because of the recent advances in technology, most training programs now focus on PPV, and they vary with respect to their emphasis on segmental, radial, and encircling SB, either alone or in combination with vitrectomy, and pneumatic retinopexy (PnR).

However, there is a paucity of adequately powered randomized clinical trials comparing the functional outcomes associated with the various surgical techniques of RRD repair. Furthermore, the most commonly used measure of success has been the relatively basic and rudimentary outcome of single-operation reattachment rate. We now know that retinal reattachment is necessary, but not sufficient, to achieve the best possible outcomes for our patients.

Until recently, we have been limited in our ability to assess the "integrity" of the retinal reattachment and have had limited evidence regarding which techniques provide patients with the best functional results.

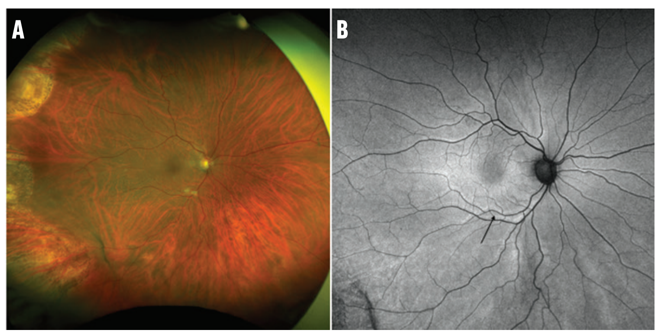


Figure 1. This ultra-widefield color photograph demonstrates a reattached retina following PPV for RRD repair (A). The ultra-widefield fundus autofluorescence image of the same patient shows multiple retinal vessel printings (black arrow, B), indicating that the retina has been displaced from its original position. This patient has had a low-integrity retinal attachment.

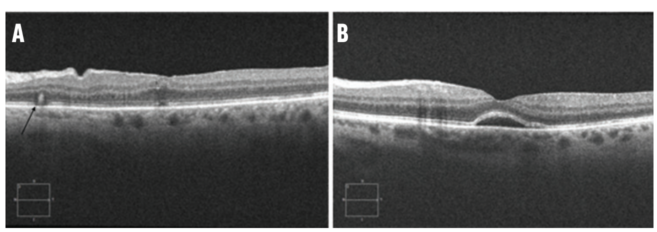


Figure 2. The cross-sectional OCT in a patient following PPV for RRD repair demonstrates a prominent outer retinal fold (black arrow, A). In another patient, OCT reveals a persistent subfoveal fluid bleb (B).

## RRD AND EVIDENCE-BASED MEDICINE

We have entered a new era in RRD repair guided by a greater emphasis on evidence-based medicine and significant advances in accessible multimodal imaging. Together, these two factors have enabled us to move closer to determining

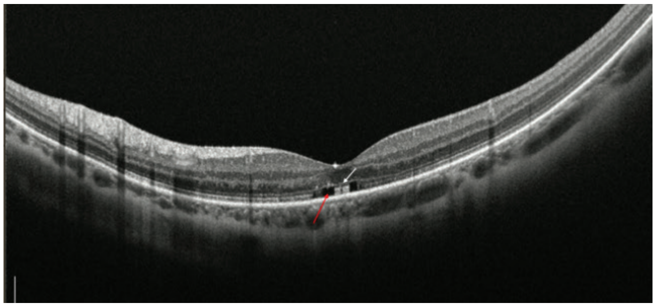

Image courtesy of Barbara Parolini, MD

Figure 3. The cross-sectional OCT in a patient following PPV with an intact foveal external limiting membrane (white arrow) demonstrates discontinuity of the ellipsoid zone and interdigitation zone (red arrow).

the best possible treatment approach for a given patient when considering both functional and anatomic outcomes.

*Functional outcomes* include visual acuity, metamorphopsia, aniseikonia, and vision-related quality of life.

*Anatomic outcomes* include not only single-operation reattachment rate but also the final reattachment rate in addition to the presence or absence of retinal displacement (Figure 1), outer retinal folds (Figure 2a), persistent subretinal fluid blebs (Figure 2b), discontinuity of the external limiting membrane, and ellipsoid zone integrity (Figure 3), among other imaging biomarkers. These anatomic outcomes of integrity, some of which are not visible on clinical examination with indirect ophthalmoscopy, can be assessed with multimodal imaging.

Although we are early in our understanding of how abnormalities in the anatomic outcomes of integrity impact patients, stretching, folding, or lack of continuity in retinal layers may have some impact on functional outcomes. Knowing why these anatomic abnormalities occur can help us begin to understand how they may be prevented or minimized, leading to refinements in our surgical techniques.

## A DIFFERENCE IN INTEGRITY

The PIVOT trial, a single-center randomized trial of 176 patients, compared PPV to PnR for patients with RRD who met specific inclusion/exclusion criteria.[1] The study found that patients treated with PnR had superior ETDRS visual acuity at every postoperative study visit, including the 1-year primary endpoint, compared with patients who were treated with PPV. Furthermore, patients treated with PnR had superior vision-related quality of life in the first 6 months.[2] Surprisingly, patients treated with PnR had less vertical metamorphopsia compared with those treated with PPV.

This finding is intriguing, considering postoperative vertical metamorphopsia is most likely the result of a structural and/or functional abnormality of the photoreceptors, and raises the question, “is there a difference in the integrity of retinal reattachment with different surgical procedures?”

## THE ANSWER IS IN THE DATA

The first step in answering this question is reviewing a series of studies that assessed whether the retina was reopposed as closely as possible to its original position following retinal reattachment. A multicenter retrospective study found that those treated with PPV had a substantially greater risk of retinal displacement compared with patients who underwent PnR.[3]

On fundus autofluorescence imaging, hyperautofluorescent lines indicating the location of retinal vessels before the RRD were compared with the new location of the corresponding retinal vessels after RRD repair. These lines are hyperautofluorescent because they occur where the retinal pigment epithelium (RPE)—previously shielded by retinal vessels—became exposed to light following reattachment of the retina in the presence of retinal displacement. The prior lack of exposure to light likely results in a different composition of fluorophores and metabolic activity in the RPE, which leads to a difference in the autofluorescence. We refer to a case with retinal displacement as a low-integrity retinal attachment (LIRA) and a case without retinal displacement as a high-integrity retinal attachment (HIRA).

Further multicenter studies have confirmed the substantially greater risk of retinal displacement associated with PPV compared with PnR.[4] They have also demonstrated that patients with LIRA have a greater risk of aniseikonia compared with patients with HIRA.[4] Following retinal detachment repair, many patients complain of micropsia; retinal displacement may stretch the retina and causes changes in the spacing between photoreceptors, leading to subsequent changes in the perceived size of an object.

Following the studies on retinal displacement, other anatomic outcomes of retinal reattachment integrity were investigated.[5] Eyes in the PIVOT trial were imaged with spectral-domain OCT at 1 year, and a higher risk of ellipsoid zone and external limiting membrane discontinuity was found in eyes treated with PPV compared with those treated with PnR.[5] In addition, other post-hoc analyses of the PIVOT trial showed that the rate of outer retinal folds was higher in the PPV group compared with the PnR group at 1 month (34.1% vs 14.3%, $P = .034$). Eyes that underwent PPV and presented with outer retinal folds at 1 month had reduced visual acuity at 1 year compared with PPV eyes without outer retinal folds (62.8 ± 24.7 ETDRS vs 75.4 ± 9.2 ETDRS, $P = .04$).[6]

Another area of interest has been how exactly the retina reattaches. Until recently, the understanding of the physiology of retinal reattachment in vivo was limited. What information we had came from landmark studies in owl monkeys in the 1960s by Machemer.[7] Recently, the in vivo physiology of retinal reattachment in humans was characterized using swept-source OCT imaging of eyes that

**THE MOST COMMONLY USED MEASURE OF SUCCESS HAS BEEN THE RELATIVELY BASIC AND RUDIMENTARY OUTCOME OF SINGLE-OPERATION REATTACHMENT RATE. RETINAL REATTACHMENT IS NECESSARY, BUT NOT SUFFICIENT, TO ACHIEVE THE BEST POSSIBLE OUTCOMES FOR OUR PATIENTS.**

underwent PnR.[8] Five stages of retinal reattachment, from the initial approach of the retina toward the RPE (stage 1) to the restoration of the foveal bulge (stage 5c), were described. By studying these stages in detail, we are able to understand how certain anatomic abnormalities, such as outer retinal folds and persistent subfoveal fluid blebs, can form and, in some cases, be avoided.

## WHAT WE LEARNED

These data have taught us important lessons about the comparison of outcomes associated with PPV versus PnR and how PPV may be modified to potentially minimize the risk of adverse anatomic outcomes of integrity such as retinal displacement and outer retinal folds.

In PnR, the technique involves a slow and natural resolution of subretinal fluid after closure of the retinal break(s) and a small-volume gas tamponade. These two features may serve to reduce the risk of unfavorable anatomic outcomes of integrity following PnR. The corollary is that these factors also may be modified in PPV in an attempt to improve outcomes.

Minimal gas vitrectomy and minimal gas vitrectomy buckle have been developed to reduce the risk of retinal displacement following RRD repair in certain appropriate cases.[9,10] In these procedures, although a complete PPV is performed, the retina is left detached and no fluid-air exchange is performed. A small gas bubble is injected at the end of PPV after the wounds are closed. The patient is then positioned in a manner similar to PnR. The retinal break is treated with cryopexy during surgery or with laser retinopexy once the retina is reattached; this is facilitated by endodiathermy marking of the break(s) at the time of PPV. In cases with inferior breaks, a segmental buckle is added. These procedures may serve to reduce the risk of retinal displacement, outer retinal folds, and ellipsoid zone/external limiting membrane discontinuity associated with PPV.

We are entering an exciting time in vitreoretinal surgery, where we may be guided by multimodal imaging and randomized trial data to optimize case selection and surgical techniques, with subsequent improvements in the integrity of retinal attachment and functional outcomes for patients. Looking beyond the single-procedure reattachment rate will serve us and our patients well. ■

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**RAJEEV H. MUNI MD, MSC, FRCSC**
- Vitreoretinal Surgeon, St. Michael's Hospital/Unity Health Toronto, Toronto, Ontario
- Vice-Chair Clinical Research, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario
- rajeev.muni@gmail.com
- Financial disclosure: Advisory Board (Allergan, Bayer, Novartis, Roche); Consultant (Alcon, Novartis); Research Funding and Grants (Bayer, Novartis, Roche)

**INGRID U. SCOTT, MD, MPH | SECTION EDITOR**
- Jack and Nancy Turner Professor of Ophthalmology, Professor of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania
- iscott@pennstatehealth.psu.edu
- Financial disclosure: None

# A PEEK AT THE COMPLEMENT PATHWAY


Experts share what we have learned so far, and how it might impact clinical practice—soon.

**AN INTERVIEW WITH PETER K. KAISER, MD, AND CHARLES C. WYKOFF, MD, PHD**

The complement pathway has been a hot topic in retina research for years. As several programs work their way through phase 3 trials, it may become increasingly relevant for the clinic. *Retina Today* sat down with two experts in the field, Peter K. Kaiser, MD, and Charles C. Wykoff, MD, PhD, to find out what all the fuss is about.

### *Retina Today*: How has our understanding of the complement pathway evolved over the years?

**Peter K. Kaiser, MD:** The complement system, part of our innate immune system, is conserved across species and is designed to combat bacteria and foreign invaders. There are three activation pathways. The classical pathway is activated by antibodies binding to bacteria, initiating the cascade producing C3- and C5-convertase that leads to the formation of membrane attack complex (MAC) on the bacterial surface or activation of macrophages and inflammasomes via C3a and C5a. The MAC produces open pores in the cell membrane, thereby killing the bacteria.

The lectin pathway is similar, except you don't need antibodies. The body simply recognizes epitopes on a bacterial surface, which initiates the same cascade.

The most interesting pathway is the alternative pathway because our body was smart enough to say, "I don't know what I'm going to be up against, so, I'm going to constantly activate the complement cascade, and place activated C3b, which is called opsonization, on everything I see." And then the body inactivates the C3b through complement factor H (CFH) and complement factor I (CFI) to protect host cells from being damaged by the system.

We've always known that inflammation plays a role in AMD. Genome-wide association studies first identified that mutations in the gene coding CFH were associated with an increased risk of macular degeneration. Since then, other parts of the complement cascade have been identified to increase the risk. But more importantly, histopathologic staining around drusen, geographic atrophy (GA), and choroidal neovascularization reveals multiple components from the complement cascade. But we don't know which pathway is most involved. Researchers started to test the theory that blocking complement factors could slow AMD, and they attacked complement using drugs from cancer and other indications. Those studies weren't designed to test the drugs for ophthalmic use, and many of them failed. In addition, large prospective phase 3 studies with a complement factor D inhibitor, lampalizumab (Genentech/Roche), didn't meet their primary endpoints.

That really made us question whether we should attack complement. Maybe it was too late in the process, and we needed to do it earlier, or maybe we weren't attacking it in the right place. But since then, we have discovered newer drugs that have had better results.

### *RT*: Why should busy retina surgeons brush up on the complement pathway now?

**Charles C. Wykoff, MD, PhD:** GA remains the largest unmet need in most retina clinics across the United States. We have nothing to treat this disease, and multiple studies have failed. Currently, all of the programs in late-stage human trials that are promising involve selective inhibitors of different steps within the complement cascade.

It's important that physicians understand the mechanisms of action of these therapies that are likely to be clinically available in a few years. However, while retina specialists are familiar with the mechanisms of action of anti-VEGF drugs and some of the nuances between VEGF-A, other VEGF family members, and the different VEGF receptors, the complement cascade is much more complicated.

The complement cascade involves the interaction of dozens of membrane-bound and fluid-phase proteins that are produced both in the liver and locally within the eye. Furthermore, many of the key molecules cleaved during complement propagation, including C3 and C5, have breakdown products with multiple physiologic functions. From a basic biology perspective, even the scientists working on elucidating the nuances of each of these molecules are clear that we don't understand everything about the complement pathway. We are developing new therapies within an incomplete body of knowledge. Nonetheless, it's important that physicians understand the key molecules and mechanisms that we are targeting because these medicines will likely become relevant to clinical practice in the near future.

### *RT*: Which therapeutics are showing promise?

**Dr. Wykoff:** The ultimate goal is to prevent the development of GA before it begins, but for now, the molecules in late-stage development are all attempting to slow the progressive enlargement of areas of GA. One trial program, GATHER, involves avacincaptad (Zimura, Iveric Bio), an inhibitor of C5 cleavage. The first pivotal trial studying avacincaptad, GATHER1, was positive, and the ongoing phase 3 GATHER2 trial is anticipated to have data this year.

The other program involves pegcetacoplan (Apellis Pharmaceuticals), an inhibitor of C3 cleavage. Pegcetacoplan was studied in the FILLY phase 2 trial, and in 2021, 1-year data was presented from the phase 3 DERBY and OAKS trials, which involved 1,258 patients; in OAKS, pegcetacoplan met the primary endpoint and in DERBY pegcetacoplan did not meet the primary endpoint.

There are other ongoing trial programs as well, including programs aiming to inhibit the MAC, C1Q in the classical pathway, complement factor D (one of which is an oral formulation), and additional C3 inhibitors; finally there are programs aiming to increase the down-regulators of the pathway, including CFH and CFI.

As incredibly promising as these trials are, their objectives may be disheartening for some patients; many patients with GA want to see better, especially those with foveal involvement. But the reality is that the therapeutics in phase 3 trials appear to be able to slow GA progression, probably not stop it all together, at least within the time frame of the studies to date. We are interested to see, as we treat these patients consistently for longer periods of time, if the differential between no treatment and treatment will grow.

Overall when considering the current data from both avacincaptad and pegcetacoplan, it appears that inhibition of the complement cascade at C3 or C5 leads to a slowing of GA growth by about 15% to 30%, with a greater reduction observed among patients with extrafoveal lesions, a phenotype well-recognized to be associated with a more rapid rate of GA growth than lesions that involve the fovea.

### *RT*: What are some of the challenges researchers face?

**Dr. Kaiser:** Our regulatory environment only allows us to get a drug approved that prevents photoreceptor loss, which in this case means preventing GA growth. We know that the complement cascade is involved early in AMD, but proving that these molecules prevent photoreceptor loss requires a considerably longer study. You need to take patients with intermediate AMD, for example, and prove that they don't develop GA. This study would take 2 or 3 years.

Both of the drugs currently in phase 3 have shown that they can prevent the progression of incomplete retinal pigment epithelial (RPE) and outer retinal atrophy (iRORA) to complete RPE and outer retinal atrophy (cRORA), or GA. They also can prevent progression from intermediate AMD to iRORA or cRORA. Thus, it appears that both drugs, even though their primary outcomes have nothing to do with iRORA or conversion of drusen into iRORA, have a mechanism of action that works earlier than what is being tested in phase 3 clinical trials, which hopefully means we will start to treat patients earlier if these drugs get approved.

In addition, companies will hopefully develop longer-acting agents in the future. One company is using gene therapy to deliver recombinant CFI, which should help patients with the mutation have lifelong treatment against AMD. We know that complement inhibition is not an episodic type of treatment, it's going to be lifelong. The first step is getting a treatment to work, and the second area of intense research now is looking at ways to make that last longer, much longer.

### *RT*: What are you most excited about as research continues for therapies targeting the complement pathway?

**Dr. Kaiser:** Complement modulation is an incredibly exciting avenue. We have a massive unmet need, and we are finally starting to see something that appears to work. The teaching has always been that there's no treatment for GA, which is true right now. But we hope to change that soon. ■

**CHARLES C. WYKOFF, MD, PHD**
- Director of Research, Retina Consultants of Texas/Retina Consultants of America, Houston, Texas; Deputy Chair for Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston, Texas
- ccwmd@retinaconsultantstexas.com
- Financial disclosure: Research Grants/Scientific Advisor (Apellis, Iveric, Gyroscope, NGM)

**PETER K. KAISER, MD**
- Chaney Family Endowed Chair in Ophthalmology Research; Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine; staff surgeon in the vitreoretinal department at the Cole Eye Institute, Cleveland Clinic; founding director of the Digital Optical Coherence Tomography Reading Center at the Cole Eye Institute, all in Cleveland, Ohio
- pkkaiser@gmail.com
- Financial disclosure: Advisory Board/Consultant (Aerie, Aerpio, Alcon, Allegro, Allergan, Annexon Biosciences, AsclepiX, Bayer, Bausch + Lomb, Biogen Idec, Boerenger Ingelheim, Carl Zeiss Meditec, Clearside, Eyevensys, Formycon/BioEq GmbH, Galecto, Galimedix, Glaukos, iRenix, jCyte, Kala, Kanghong, Kodiak, NGM Biopharmaceuticals, Novartis, Ocugenix, Oculis, Regenexbio, Retinal Sciences, Roivant, Santen, SciFluor, Shire, Spark, Stealth, Takeda, Verana Health [Digisight])

# UPDATES ON PEDIATRIC RETINA CARE FROM THE PODIUM

The advances in retina are changing how we approach diagnosis and treatment, even for our youngest patients.

LECTURES BY R.V. PAUL CHAN, MD, MSC, MBA, FACS

*We had an amazing start to our 49th annual Aspen Retinal Detachments Society Meeting (ARDS). It was a pleasure to bring R.V. Paul Chan, MD, MSc, MBA, FACS, back to the podium to talk about a topic on which he is the world's authority: pediatric retinal diseases. Dr. Chan is one of our youngest and newest chairmen for ARDS and has been a major thought leader in the field of pediatric retina.*

*Our 50th anniversary meeting is just around the corner on March 5-9. If you haven't already registered, head to https://aspenretina.com for more information. Get ready for more slopes, slides, and socializing.*

**- Timothy G. Murray, MD, MBA**

At the 2021 ARDS meeting in Snowmass, Colorado, Dr. Chan delivered two engaging lectures focused on recent changes that impact how retina specialists diagnose and treat pediatric patients with retinal diseases such as retinopathy of prematurity (ROP). Here, we summarize the discussions.

## LASER VERSUS ANTI-VEGF

How do we transition from laser to anti-VEGF for pediatric patients? Many treatment options are available, and it can be a challenging decision when determining which is best for a patient, according to Dr. Chan during his lecture on "Treatment of Pediatric Retina Patients in the Era of Laser and Anti-VEGF." Dr. Chan presented the research and clinical experiences that shape how retina specialists are answering that question.

### Where Do We Stand in the Treatment of ROP?

The RAINBOW study prospectively evaluated the use of ranibizumab (Lucentis, Genentech/Roche) for ROP and is now on a 5-year extension study. Data show that patients treated with ranibizumab had good anatomical outcomes.[1]

In addition to the RAINBOW study, there are also the ongoing FIREFLEYE and BUTTERFLEYE studies for 0.4 mg aflibercept (Eylea, Regeneron).[2] "Now, all these questions that we've had for over a decade, what drug, what dose, and so forth, they're being addressed," Dr. Chan stated.

According to Dr. Chan, David K. Wallace, MD, and PEDIG, in collaboration with the DRCR Retina Network, are looking at low-dose bevacizumab (Avastin, Genentech/Roche) and its efficacy for ROP compared with laser in ROP3. They are also looking at more aggressive disease and more posterior disease in ROP4. These studies are underway.

### International Endeavors

With the advent of anti-VEGF therapy, our access to treatment has improved where resources may have been limited. "From my own experience and working with my collaborators around the world, anti-VEGF agents have given many children hope for vision when previously they may have gone blind," Dr. Chan shared. "Even though laser is effective, many areas of the world don't have reliable access to laser or pediatric anesthesia. There is an increasing number of children who are being born premature, so there continues to be children at risk of developing ROP around the world."

With anti-VEGF treatment, clinicians can have high success rates in promoting regression of ROP. So, should we change our treatment criteria? Dr. Chan shared his thoughts. "We've went from doing laser for everyone who required treatment to now having anti-VEGF at our disposal for certain cases," Dr. Chan explained. "What we're learning now is that laser is still a good option. I continue to use laser for most cases of zone II, stage 3, plus disease. For aggressive ROP, I consider using anti-VEGF agents." The literature also shows that there can be success in treating with anti-VEGF plus laser at some point, he added.

Still, it's difficult to measure safety in these premature children. ROP is appearing in infants who would not have survived a decade ago, raising the question of increased concern for a safety signal due to the patient's age, he noted.

Back in 2006, clinicians were discussing whether anti-VEGF treatment was ethical in infants. Now, those discussions have turned to what are the ethics of *not* using an anti-VEGF drug, Dr. Chan said. Clinicians have enough experience to offer parents a detailed informed consent about the unknown—a conversation worth having because it works in many situations, especially for ROP. The field must look at redefining the treatment criteria, especially for pediatric retinal diseases.

## CLASSIFYING ROP

The International Classification of Retinopathy of Prematurity (ICROP), composed of 34 faculty from six continents, creates a standard nomenclature for classification of ROP. It was first published in 1984, expanded in 1987, and revisited in 2005 and 2021.[3]

In his second talk, Dr. Chan shared the major updates to the ICROP, including redefining and refining classification metrics, such as posterior zone, notch, reactivation, regression, subcategorization of stage 5, and recognition of a plus disease spectrum.

### AROP Versus APROP

Often, "what we defined as aggressive *posterior* ROP (APROP) didn't fall posteriorly," Dr. Chan explained. These changes can occur in larger and older preterm infants, and present anterior to the posterior retina. They are aggressive and progress rapidly. The change from APROP to *aggressive* ROP (AROP) focuses more on the tempo of the disease and the appearance of the vascular abnormalities, not necessarily the location. Although it often occurs posteriorly, Dr. Chan shared, the term *AROP* is now preferred.

### Reactivation and Regression Patterns

Clinicians have been more familiar with defining reactivation after laser, but there has been some heterogeneity in what they define as reactivation after anti-VEGF treatment. ICROP3 advises the use of two separate terms when describing later phases of ROP: *regression*, which refers to disease involution and resolution; and *reactivation*, which refers to recurrence of acute phase features and can typically be seen more frequently after anti-VEGF treatment.[3]

### Plus Disease Spectrum

Clinicians have relied heavily on the standard plus disease photo, Dr. Chan stated, but with better imaging and more experience, plus disease has been recognized as a spectrum. ICROP3 recommends that this spectrum be determined from vessels within zone I, rather than from only vessels within the field of narrow-angle photographs and rather than from the number of quadrants of abnormality.[3,4]

Pre-plus disease is what even expert ROP clinicians often disagree on. This severity scale creates a progressive discussion about the plus disease spectrum.

WATCH IT NOW

ROP in the Era of Anti-VEGF

### Stage 5

With improved imaging technology that is more accessible for use with children, clinicians can detect changes earlier, especially in stage 4 disease, Dr. Chan said. ICROP3 has recently added subcategories for stage 5: stage 5A, in which the optic disc is visible by ophthalmoscopy; stage 5B, in which the optic disc is not visible secondary to retrolental fibrovascular tissue or closed-funnel detachment; and stage 5C, in which findings of stage 5B are accompanied by anterior segment abnormalities.[3]

### Notch

The ICROP defines three zones of ROP, although we still classify ROP by the most posterior zone. Dr. Chan discussed the definition of *posterior zone II*, which is a region that is 2 disc diameters peripheral to the zone I border and may potentially be a more worrisome disease than ROP in the more peripheral zone II. Zone II is a ring-shaped region extending nasally from the outer limit of zone I to the nasal ora serrata and with a similar distance temporally, superiorly, and inferiorly.[3,4]

The term *notch* describes an incursion by the ROP lesion of 1 to 2 clock hours along the horizontal meridian into a more posterior zone than the remainder of the retinopathy. It is documented as "secondary to notch."

## CONCLUSION

Dr. Chan concluded his lecture by affirming the forward momentum of the field, given the new technology, treatments, and 35 years of collective learning. ■

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# Steroid Therapy for The Long Haul


Many sustained-release options are available to help quell inflammation. Here's what you need to know.

BY KAPIL MISHRA, MD, AND THEODORE LENG, MD, MS

Sustained-release corticosteroids have become a mainstay in the retina specialist's armamentarium for an array of retinal diseases. Due to their effects on several pathways, steroids have antiinflammatory, antiangiogenic, and antipermeability properties that are advantageous for treating many retinal diseases, including diabetic macular edema (DME), retinal vein occlusion (RVO), noninfectious posterior uveitis, and cystoid macular edema (CME). Because long-term use of systemic corticosteroid therapy carries with it significant side effects, local ocular therapy has proven valuable because of its high efficacy and safe systemic profile. The push for longer-acting therapeutics has garnered us several long-duration corticosteroid therapies to choose from (Figure). This article summaries your options (Table).

## TRIAMCINOLONE ACETONIDE

Triamcinolone acetonide (TA), a potent glucocorticoid, is a white crystalline powder that is insoluble in water. The two most common preparations are kenalog-40 (40 mg/ml), which is off-label for intraocular use but is often used as a sub-Tenon's injection or intravitreal injection for an array of retinal diseases, and preservative-free Triesence (40 mg/ml, Alcon), which is FDA-cleared for intraocular use.

A recent addition to the ocular steroid therapy space is suprachoroidal Xipere (triamcinolone acetonide injectable suspension, Bausch + Lomb) which gained FDA approval in October 2021 for the treatment of macular edema associated with uveitis. Approval came following results of the PEACHTREE study that included 160 patients.[1] Patients were enrolled if they had noninfectious uveitis, no other ocular disease, and central subfield thickness greater than 300 µm. Both medication and sham groups were treated at day 0 and week 12, and results showed that the suprachoroidal arm gained 15 letters or more from baseline in 46.9% of eyes compared with 15.6% in the sham group at week 24 ($P < .001$). Central subfield thickness was reduced by 153 µm in the suprachoroidal group compared with 18 µm in the sham group ($P < .001$). IOP elevation was seen in only 11.5% of eyes after two suprachoroidal injections.

## DEXAMETHASONE IMPLANT

Ozurdex (Allergan), a biodegradable 0.70 mg dexamethasone implant given as an intravitreal injection via a 22-gauge needle, is FDA-cleared for DME, macular edema secondary to branch or central RVO, and noninfectious posterior uveitis. After implantation, dexamethasone is detectable in the vitreous 6 months following injection; however, peak concentration is around 2 months.

## AT A GLANCE

- Local ocular therapy, as opposed to systemic steroid therapy, has proven valuable because of its high efficacy and safe systemic profile.
- A recent addition to the ocular steroid therapy space is suprachoroidal Xipere (triamcinolone acetonide injectable suspension, Bausch + Lomb).
- Retina specialists have been aware of fluocinolone implants for some time, given that the first insert gained FDA approval in 2005 for the treatment of noninfectious posterior uveitis.

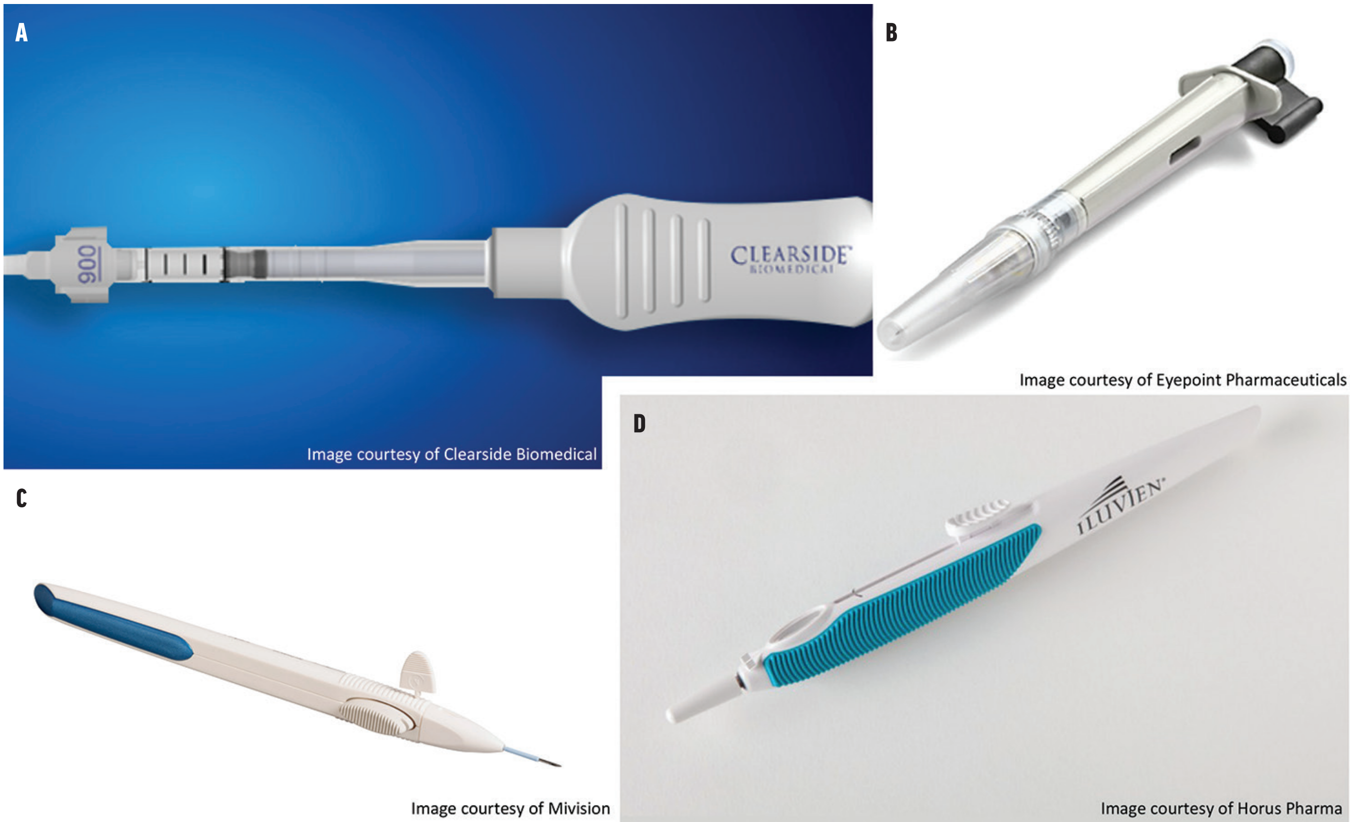


**Figure. The nonsurgical long-duration steroid options each have a specialized injector to ensure safe drug delivery. Xipere uses the SCS microinjector (Clearside Biomedical) that comes with both a 900 µm and 1,100 µm length needle (A). The tip of Yutiq's single-use preloaded applicator should be oriented above the horizontal plane during the procedure to prevent the implant from falling out of the applicator (B). Ozurdex's applicator uses an accordion-style mechanism (C). Iluvien's preloaded applicator uses a spring-free mechanism to expel the implant (D).**

The MEAD study assessed the 0.35 mg and 0.70 mg dexamethasone implants compared with sham in patients with DME and found a 15-letter improvement or more compared with baseline for 22.2% in the 0.70 mg group, 18.4% in the 0.35 mg group, and 12.0% in the sham group ($P < .018$).[2] Mean reduction in central subfield thickness was significantly higher in the dexamethasone groups compared with sham, and only three patients in the implant groups required glaucoma surgery.

The GENEVA trial was a pivotal study comparing the 0.70 mg dexamethasone implant with sham for macular edema due to RVO and found that the dexamethasone groups produced significantly greater improvements in visual acuity and achieved a faster 15-letter improvement compared with sham.[3] The largest differences between groups took place on days 30, 60, and 90, although visual acuity gains were diminished by day 180, suggesting low levels of dexamethasone 6 months following injection. Of patients in the dexamethasone group, 22.9% were on IOP-lowering medications at study end with a majority taking only one medication. Similar to MEAD, only three patients required incisional glaucoma surgery.

Finally, the HURON study assessed 0.35 mg and 0.70 mg dexamethasone implants for noninfectious intermediate or posterior uveitis and found a vitreous haze score of 0 at week 8 in 47% of eyes in the 0.70 mg group, 36% in the 0.35 mg group, and 12% in the sham group ($P < .001$), as well as a significantly higher proportion of eyes with a 15-letter or more gain in the treatment groups.[4]

## FLUOCINOLONE ACETONIDE IMPLANTS

Fluocinolone acetonide is a synthetic corticosteroid with similar potency to dexamethasone and is used in several long-acting steroid implants.[5-7] Retina specialists have been aware of fluocinolone implants for some time, given that the first insert, Retisert (0.59 mg fluocinolone acetonide, Bausch + Lomb) gained FDA approval in 2005 for the treatment of noninfectious posterior uveitis. This surgically-implanted device can release higher concentrations of steroid than the intravitreal implants that have come after it, particularly early in the treatment course. Recent clinical data suggest that the Retisert implant is still a reasonable option for the treatment of uveitis.[8]

The MUST follow-up study was a 7-year observational study of an initial cohort that was randomized to receive either systemic antiinflammatory treatment or the Retisert implant.[8] The 2-year results demonstrated that patients with the Retisert implant fared better in terms of visual acuity and uveitis activity; however, the 7-year follow-up data appears to favor systemic therapy. It is worth noting that after the

**TABLE. LONG-ACTING STEROID OPTIONS**

| | Indication | Delivery | Duration/Efficacy |
|---|---|---|---|
| **Triamcinolone Acetonide** | | | |
| Sub-Tenon's Injection (40 mg/ml) | Macular edema associated with uveitis, cystoid macular edema from various etiologies, intermediate/posterior uveitis | Sub-Tenon's space; most common medication used is kenalog-40 delivered in 0.5 mL volumes | 2 to 3 months; duration may vary due to variability of kenalog crystal sizes |
| Preservative-Free Triesence (40 mg/ml, Alcon) | Macular edema associated with uveitis, diabetic macular edema, macular edema secondary to retinal vein occlusion | Intravitreal | 4 to 6 weeks (less for vitrectomized eyes); better BCVA and OCT thickness in macular edema compared with sub-Tenon's |
| Xipere (Bausch + Lomb) | Macular edema associated with uveitis | Suprachoroidal, 0.1 mL administered using a 30-gauge needle | Treatment response noted up to 9 months in 50% of patients[2] |
| **Dexamethasone** | | | |
| Ozurdex (0.7 mg, Allergan) | Diabetic macular edema, retinal vein occlusion-associated macular edema, noninfectious posterior uveitis | Intravitreal, bioerodable | 3 to 4 months |
| **Fluocinolone Acetonide** | | | |
| Iluvien (0.19 mg, Alimera Sciences) | Diabetic macular edema | Intravitreal, nonbioerodable | Up to 36 months |
| Yutiq (0.18 mg, EyePoint Pharmaceuticals) | Noninfectious posterior uveitis | Intravitreal, nonbioerodable | Up to 36 months |
| Retisert (0.59 mg, Bausch + Lomb) | Chronic noninfectious posterior uveitis, patients who cannot tolerate systemic therapy | Surgically implanted and sutured at pars plana | Approximately 2.5 years; uveitis recurrence rate decreased by more than 50% at 34 weeks |

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2-year study, specific treatment patterns were not mandated, and patients could cross over between arms. Also, most Retisert patients only received one implant over the 7 years, while the majority of patients in the systemic group were on active therapy at the end of 7 years, suggesting that patients in the Retisert group were undertreated later in the study.

Two newer intravitreal implants are FDA-approved for retinal conditions: Iluvien (0.19 mg, Alimera Sciences) and Yutiq (0.18 mg, EyePoint Pharmaceuticals).

Iluvien is a nonbioerodable implant that releases a low dose (0.20 ug/day) of steroid into the vitreous for 36 months. This implant gained FDA approval in 2014 for the treatment of DME following efficacy results in the FAME study.[5] Patients with persistent DME despite laser treatment were randomized to a low-dose (0.20 ug/day) insert, high-dose (0.50 ug/day) insert, or sham. The primary endpoint was the percentage of patients with improvement in 15 or more letters at 2 years. The treatment groups demonstrated this outcome in 28% of patients compared with 16% in the sham group ($P$ = .002). The implants also showed a rapid and sustained reduction in the central subfield thickness compared with sham. As with other steroid implants, cataracts and elevated IOP were the most common adverse events. Of patients who received the low-dose insert (the one that is currently available) in the FAME study, 3.7% required incisional glaucoma surgery.

A retrospective, real-world study of Iluvien noted that following the implant, 63% of eyes did not require additional DME treatments up to month 24. Rates of incisional glaucoma surgery were lower than what was reported in the FAME study, and patients who lacked a significant IOP elevation with prior steroid use were unlikely to demonstrate an IOP spike following the implant.

The other nonbioerodable intravitreal fluocinolone acetonide implant, Yutiq, is FDA-approved for the treatment of noninfectious posterior uveitis and is also designed to slowly release the drug over 36 months. Two multicenter, randomized controlled trials assessing response over 36 months

| | Contraindications | Complications | Adverse Events |
|---|---|---|---|
| | | | |
| | Active ocular infection, advanced glaucoma | Subconjunctival hemorrhage, central retinal artery occlusion, globe perforation, ptosis, strabismus | Elevated IOP (although less likely than intravitreal options);[1] cataract formation |
| | Active ocular infection, advanced glaucoma | Postinjection endophthalmitis, sterile endophthalmitis (if kenalog was used) | Immediate IOP spike following injection; 26% with uveitic macular edema had at least a 10-point increase in IOP from baseline;[1] cataract formation |
| | Active ocular infection, known hypersensitivity to triamcinolone acetonide | Resistance during injection due to not being in the correct anatomical space; injection site pain | IOP elevation > 10 mm Hg from baseline in 14.3%;[2] lower rates of cataract compared with intravitreal options |
| | | | |
| | Active ocular infection, advanced glaucoma, or when posterior lens capsule is not intact (risk of anterior chamber migration) | Postinjection endophthalmitis, hypotony (from wound leak) | High incidence of cataract development compared with sham; IOP rise typically 4 to 6 weeks following injection |
| | | | |
| | Active ocular infection, avoid in aphakia | Postinjection endophthalmitis | 18.4% had IOP > 30 mm Hg after 3 years,[3] 80% develop cataract after 3 years |
| | Active ocular infection, avoid in aphakia | Postinjection endophthalmitis | 56% of patients developed a cataract within 1 year; 43% were on at least one IOP-lowering medication; 2% required glaucoma surgery[4] |
| | Active ocular infection; consider systemic therapy if patients also have systemic disease and bilateral ocular disease | Surgical complications of hypotony, vitreous hemorrhage; Postoperative complications of wound site erythema, dehiscence, hypotony (9.4% of eyes), scleral thinning over implant[5] | Within 3 years, 77% of patients require IOP drops, and 37% require filtering procedures;[5] within 3 years nearly all phakic eyes require cataract surgery |

demonstrated significantly lower uveitis recurrence rates compared with sham (65.5% vs 97.6%; $P < .001$).[7] More eyes in the treatment group had a greater than 15-letter increase and improved macular edema compared with sham, and IOP was similar for both study groups at month 36.

## CONCLUSION

All long-acting steroid implants require careful patient selection to mitigate the risk of elevated IOP or cataracts. With the right patient selection and careful monitoring, the implants remain valuable tools in treating various retinal diseases due to their high efficacy and durability. ■

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**THEODORE LENG, MD, MS**
- Director, Clinical and Translational Research, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, California
- Editorial Advisory Board Member, *Retina Today*
- vision.md@gmail.com
- Financial disclosure: None

**KAPIL MISHRA, MD**
- Vitreoretinal Surgery Fellow, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, California
- Financial disclosure: None

# 10 Pearls for A Successful PDS Implantation

These surgical steps can help you master this new procedure.

BY NIKA BAGHERI, MD; AUSTIN COUVILLION, MS; AND DANTE J. PIERAMICI, MD

With the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) now FDA-approved, providers and patients will have to weigh the risks and benefits of proceeding with surgical placement of the device versus continuing standard in-office intravitreal injection therapy.

All surgeons placing a PDS for the first time should receive formal training and guidance from surgical liaisons. This article serves as a guide to maximize success and avoid pitfalls during this straightforward procedure—it is not a substitute for thorough training.

Careful and meticulous surgical technique is paramount to reduce the chance of complications. The guidance presented in this article is based on the authors' collective experiences placing the PDS during clinical trials and the cumulative experience of the investigators throughout the various ongoing PDS trials. Presented here are 10 surgical pearls for successful PDS implantation.

## 1 EVALUATE THE PATIENT CAREFULLY

First, perform a careful in-office slit lamp examination to diligently inspect the surgical eye's conjunctiva for areas of thinning and/or scarring. Patients with previous glaucoma surgery involving the superior quadrants are not surgical candidates at this time. The implant is typically inserted 4 mm posterior to the limbus in the superotemporal quadrant. Do not place the implant in an alternative quadrant because no data or surgical experience supports such a decision.

A thorough preoperative assessment can help avoid serious intraoperative and postoperative issues such as conjunctival retraction or erosion with implant exposure and subsequent infection. Patients with untreated conjunctival or lid infections are not good candidates for the device until the infections are addressed. Dry eye disease was not an exclusion criterion for enrollment in the PDS trials, but patients with severe dry eyes may not make ideal candidates.

## 2 SET YOURSELF UP FOR SUCCESS

Place a valved cannula transconjunctivally using a trocar blade in the inferotemporal quadrant with an angled entry wound. We prefer to use a 25- or 27-gauge cannula. Insert an infusion line via the cannula and keep it closed. Leave ample room between the infusion and the planned implant site while simultaneously avoiding excessive inferior placement of the infusion, which can limit your ability to rotate the eye later in the procedure. Place a corneal traction suture in the superotemporal quadrant using a 7-0 polyglactin 910 (Vicryl, Johnson and Johnson) suture to

### AT A GLANCE

- All surgeons placing a port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) for the first time should receive formal training and guidance from surgical liaisons.
- Implantation of the PDS is reimbursable under CPT code 67027 with subsequent drug refills coded similarly to standard intravitreal injection (CPT code 67028).
- Think like a glaucoma specialist: the conjunctiva and Tenon's are the king and queen when it comes to reducing future implant exposure.

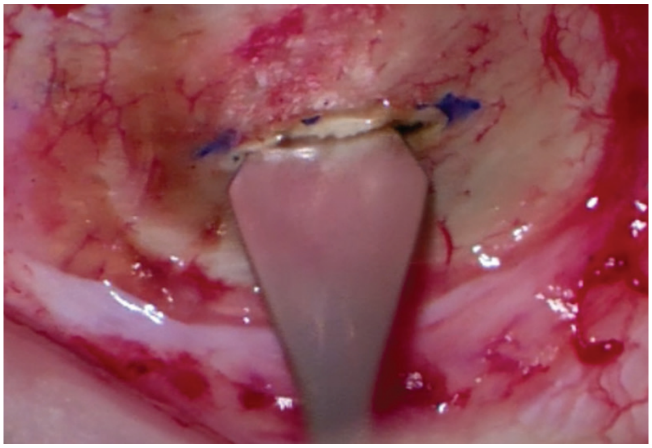

Figure 1. When entering the vitreous with the 3.2 mm slit knife, be sure to use a perpendicular, slow, and steady approach.

assist with this rotation. Adequate exposure of the superotemporal quadrant will facilitate the subsequent surgical steps. Evaluation of surgical videos during the clinical trials often revealed that inadequate exposure was associated with subsequent surgical technical difficulties.

## 3 MAKE THE PERFECT PERITOMY AND DON'T FORGET TENON'S

Fashion a superotemporal peritomy starting near the limbus measuring 6 mm by 6 mm in size, including a single relaxing radial incision. Do not leave an island of conjunctival tissue at the limbus; instead, it should be flush with and follow along the limbus. Remember that Tenon's capsule generally inserts 2 mm posterior to the limbus, and it is important to generously undermine both Tenon's and conjunctiva to maximize mobility for closure. This dissection can extend well beyond the 6 mm of the original conjunctival peritomy. Use non-toothed forceps to avoid button-holing the tissue. Think like a glaucoma specialist: the conjunctiva and Tenon's are the king and queen when it comes to reducing future implant exposure.

## 4 ENSURE HEMOSTASIS

Apply wet-field cautery to any actively bleeding or visibly engorged episcleral vessels at or near the intended insertion site; this will help to improve visualization of the sclera and allow for better detection of possible bleeding from the incision later in the procedure. Better visualization will facilitate all subsequent steps, so having control of the surgical field cannot be overstated. A little time spent with cautery can save more time later in the procedure.

## 5 LOAD THE IMPLANT PROPERLY

Fill the implant with ranibizumab using the proprietary fill needle under magnification. Fill the implant slowly over at least 5 seconds with a dome of fluid visualized at the tip. Ensure that all air bubbles have been expressed from the implant before inserting and turn the implant over to

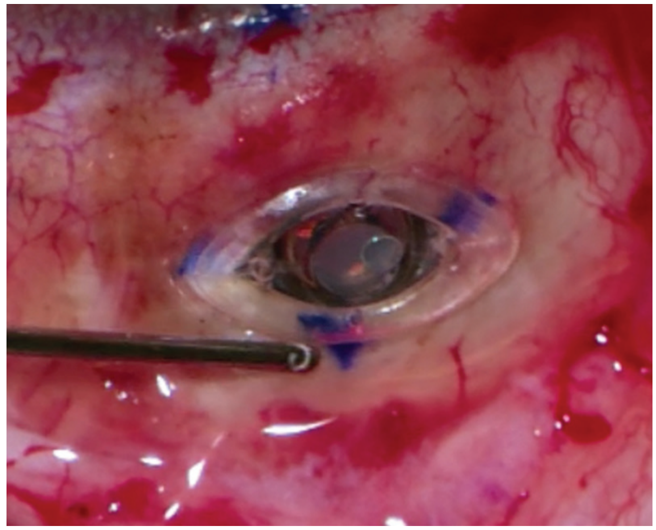

Figure 2. If necessary, perform vitrectomy around the implant after placement to remove any excessive vitreous prolapse.

visualize both sides for air. The initial fill equipment makes this step relatively straightforward, but there is always room for operator error (ie, don't forget to fill the device).

## 6 SIZE, MARK, AND CUTDOWN THE SCLERAL INCISION

Mark the sclera 4 mm posterior to the limbus at the desired implant location, and then mark a 3.5 mm length at this distance. Use a 20-gauge microvitreoretinal (MVR) blade to create a 3.5 mm lamellar incision down to bare pars plana. Hold the MVR blade perpendicular to the sclera and perform this incision under the magnification of an operating microscope. Use the incision measurement gauge that is included with the implant to confirm a correctly sized 3.5 mm incision. Oversizing the incision may increase risk of device dislocation, while undersizing may result in vitreous hemorrhage during or following insertion. If the wound is greater than 3.5 mm, place a nonabsorbable suture (8-0 or 9-0 nylon) on the side away from the relaxing conjunctival incision to make the wound 3.5 mm.

## 7 LASER METHODICALLY

Use an endolaser probe to coagulate the exposed pars plana. We prefer a 25- or 27-gauge endolaser probe with a setting of a single spot application, 300 mW power, and 1,000 ms duration. Be methodical with laser application, starting at one end of the incision and applying a single spot at a time while moving to the opposite end. The laser spots should be overlapping with special attention directed at the corners of the wound. Avoid direct contact with the target tissue, and ensure each spot is applied for a full second. Keep the area as dry as possible to allow uptake of laser in the pars plana choroid. You can detect proper ablation of the pars plana with a color change to gray or black, contraction of the pars plana tissue resulting in a perforated appearance, and visible extravasation/blebbing of vitreous fluid.

## PORT DELIVERY BASICS

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) is an ophthalmic drug delivery system that relies on a transscleral subconjunctival surgically implanted drug reservoir for continuous delivery of a customized formulation of ranibizumab. The PDS is approved for the treatment of wet AMD in patients who have had at least two previous intravitreal injections of anti-VEGF and have shown a clinical response. The device consists of the refillable 20 µL drug reservoir, a self-sealing septum, a release control element, and an extra scleral flange. Implantation of the PDS is reimbursable under CPT code 67027 with subsequent drug refills coded similarly to standard intravitreal injection (CPT code 67028).

The PDS, designed to remain in place for the life of the patient, is a therapeutic platform that could potentially be used with other pharmacologic agents as they become available.

### 8 ENTER THE VITREOUS CAREFULLY AND BE READY TO CAUTERIZE

Pass a 3.2 mm slit knife in and out through the center of the dissected sclera with a perpendicular slow and steady approach (Figure 1). Make sure not to move the blade tangentially to avoid enlarging the incision and initiating bleeding. After entering the vitreous, take a time-out during the surgery to observe for any bleeding at the edges of the incision. If there is, apply gentle fine-tip cautery to stop any bleeding without enlarging the wound.

### 9 INSERT THE IMPLANT SMOOTHLY

Stabilize the globe with a second hand and fine-toothed forceps while slowly inserting the implant in a perpendicular fashion through the full-thickness incision. Avoid taking too flat an angle and aim for the center of the vitreous cavity. Opening the infusion line once the implant tip has entered the incision is helpful to pressurize the eye and provide countertraction. After the implant is in the proper position with the gripper tips against the sclera, activate the insertion tool release button and use the closed ends of the implant insertion tool to seat the implant flush with the globe. If there was excessive vitreous prolapse that was not repositioned during the implant placement, use a vitrector to remove any excess around the implant (Figure 2).

### 10 CLOSE WITH PRECISION

The closure is one of the most important steps. Use non-toothed forceps to prevent inadvertent trauma to the conjunctiva and ensure that the conjunctiva and Tenon's capsule are reattached fully up to the limbus with a little overlap. Hydration of Tenon's will help mobilize and identify the

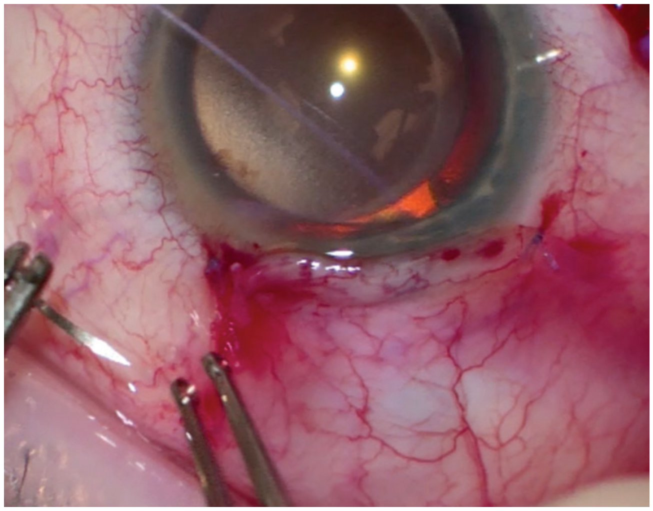

**Figure 3. During the closure, the conjunctiva and Tenon's are pulled up and secured with limbal scleral bites.**

tissues. Anchor the peritomy corners with a partial-thickness scleral bite through both conjunctiva and Tenon's (Figure 3). Close any radial 'relaxing' incisions with interrupted 8-0 Vicryl sutures. The closure should place the wound away from the implant. Test the closure at the end by ensuring that the conjunctiva cannot be easily retracted from the limbus and rests snuggly anterior to the limbus. Remove and close (if necessary) the infusion cannula, assess the implant position using indirect ophthalmoscopy, and inject subconjunctival antibiotics and corticosteroids away from the implant site.

### FINAL THOUGHTS

With proper guidance and training, appropriate patient selection, and meticulous and careful surgical techniques, you can achieve success and reduce the chance for complications when implementing this first-in-class addition to the retina toolkit. ■

**NIKA BAGHERI, MD**
- Vitreoretinal Surgeon, California Retina Consultants and Research Foundation, Santa Barbara, California
- bagheri.n@gmail.com
- Financial disclosure: Consultant, Research Grant Support (Genentech/Roche)

**AUSTIN COUVILLION, MS**
- Clinical Research Assistant, California Retina Consultants and Research Foundation, Santa Barbara, California
- Financial disclosure: None

**DANTE J. PIERAMICI, MD**
- Vitreoretinal Surgeon, California Retinal Consultants and Research Foundation, Santa Barbara, California
- dpieramici@yahoo.com
- Financial disclosure: Consultant, Research Grant Support (Genentech/Roche)

**NOW APPROVED**

# SUSVIMO

## The first and only continuous delivery treatment for nAMD[1]

Not to scale.

For more information, visit **SUSVIMO-HCP.com**

nAMD=neovascular (wet) age-related macular degeneration.

### INDICATION

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least 2 intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication.

### IMPORTANT SAFETY INFORMATION

### WARNING: ENDOPHTHALMITIS

**The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. In clinical trials, 2.0% of patients receiving an implant experienced at least 1 episode of endophthalmitis.**

### CONTRAINDICATIONS

- Ocular or periocular infections
- Active intraocular inflammation
- Hypersensitivity

### WARNINGS AND PRECAUTIONS

- The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival retraction, conjunctival erosion, and conjunctival bleb. Patients should be instructed to report signs or symptoms that could be associated with these events without delay. Additional surgical and/or medical management may be required
- Vitreous hemorrhage: Temporarily discontinue antithrombotic medication prior to the implant insertion procedure to reduce the risk of vitreous hemorrhage. Vitrectomy may be needed
- Postoperative decrease in visual acuity: A decrease in visual acuity usually occurs over the first 2 postoperative months

### ADVERSE REACTIONS

The most common adverse reactions were conjunctival hemorrhage (72%), conjunctival hyperemia (26%), iritis (23%), and eye pain (10%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see Brief Summary of full SUSVIMO Prescribing Information on adjacent page for additional Important Safety Information, including **BOXED WARNING**.

**REFERENCE**

**1.** SUSVIMO [package insert]. South San Francisco, CA: Genentech, Inc; 2021.

Genentech
*A Member of the Roche Group*



SUSVIMO™
ranibizumab injection 100 mg/mL For Ocular Implant

SUSVIMO™

ranibizumab injection 100 mg/mL For Ocular Implant

**SUSVIMO™ (ranibizumab injection) for intravitreal use via SUSVIMO ocular implant.** This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

**WARNING: ENDOPHTHALMITIS**

**The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. Many of these events were associated with conjunctival retractions or erosions. Appropriate conjunctiva management and early detection with surgical repair of conjunctival retractions or erosions may reduce the risk of endophthalmitis. In clinical trials, 2.0% of patients receiving a ranibizumab implant experienced at least one episode of endophthalmitis *[see Contraindications (4.1), Warnings and Precautions (5.1)]*.**

## 1 INDICATIONS AND USAGE

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication.

## 4 CONTRAINDICATIONS

### 4.1 Ocular or Periocular Infections

SUSVIMO (ranibizumab injection) is contraindicated in patients with ocular or periocular infections.

### 4.2 Active Intraocular Inflammation

SUSVIMO (ranibizumab injection) is contraindicated in patients with active intraocular inflammation.

### 4.3 Hypersensitivity

SUSVIMO (ranibizumab injection) is contraindicated in patients with known hypersensitivity to ranibizumab products or any of the excipients in SUSVIMO (ranibizumab injection).

## 5 WARNINGS AND PRECAUTIONS

The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, and conjunctival blebs. Patients should be instructed to report any signs or symptoms that could be associated with these events without delay. In some cases, these events can present asymptomatically. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion, and refill-exchange procedures to permit early medical or surgical intervention as necessary. Special precautions need to be taken when handling SUSVIMO components *[see How Supplied/Storage and Handling (16.3)]*.

### 5.1 Endophthalmitis

In the active comparator period of controlled clinical trials, the ranibizumab implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab (1.7% in the SUSVIMO arm vs 0.5% in the intravitreal arm). When including extension phases of clinical trials, 2.0% (11/555) of patients receiving the ranibizumab implant experienced an episode of endophthalmitis. Reports occurred between days 5 and 853, with a median of 173 days. Many, but not all, of the cases of endophthalmitis reported a preceding or concurrent conjunctival retraction or erosion event.

Endophthalmitis should be treated promptly in an effort to reduce the risk of vision loss and maximize recovery. The SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed until resolution of endophthalmitis *[see Dosage and Administration (2.9) and Adverse Reactions (6.1)]*.

Patients should not have an active or suspected ocular or periocular infection or severe systemic infection at the time of any SUSVIMO implant or refill procedure. Appropriate intraoperative handling followed by secure closure of the conjunctiva and Tenon's capsule, and early detection and surgical repair of conjunctival erosions or retractions may reduce the risk of endophthalmitis *[see Warnings and Precautions (5.5)]*.

### 5.2 Rhegmatogenous Retinal Detachment

Rhegmatogenous retinal detachments have occurred in clinical trials of SUSVIMO and may result in vision loss. Rhegmatogenous retinal detachments should be promptly treated with an intervention (e.g., pneumatic retinopexy, vitrectomy, or laser photocoagulation). SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed in the presence of a retinal detachment or retinal break *[see Dosage and Administration (2.9)]*.

Careful evaluation of the retinal periphery is recommended to be performed, and any suspected areas of abnormal vitreo-retinal adhesion or retinal breaks should be treated before inserting the implant in the eye.

### 5.3 Implant Dislocation

In clinical trials, the device has dislocated/subluxated into the vitreous cavity or has extended outside the vitreous cavity into or beyond the subconjunctival space. Device dislocation requires urgent surgical intervention. Strict adherence to the scleral incision length and appropriate targeting of the pars plana during laser ablation may reduce the risk of implant dislocation.

### 5.4 Vitreous Hemorrhage

Vitreous hemorrhages may result in temporary vision loss. Vitrectomy may be needed in the case of a non-clearing vitreous hemorrhage *[see Dosage and Administration (2.9)]*.

In clinical trials of SUSVIMO including extension phases, vitreous hemorrhages were reported in 5.2% (23/443) of patients receiving SUSVIMO. The majority of these hemorrhages occurred within the first post-operative month following surgical implantation and the majority of vitreous hemorrhages resolved spontaneously. Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. Antithrombotic medications are recommended to be temporarily interrupted prior to the implant insertion procedure. The SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed in the event of sight-threatening vitreous hemorrhage. The use of pars plana laser ablation and scleral cauterization should be performed to reduce the risk of vitreous hemorrhage.

### 5.5 Conjunctival Erosion or Retraction

A conjunctival erosion is a full thickness degradation or breakdown of the conjunctiva in the area of the implant flange. A conjunctival retraction is a recession or opening of the limbal and/or radial peritomy. Conjunctival erosions or retractions have been associated with an increased risk of endophthalmitis, especially if the implant becomes exposed. Surgical intervention (e.g., conjunctival/Tenon's capsule repair) is recommended to be performed in case of conjunctival erosion or retraction with or without exposure of the implant flange.

In clinical trials of SUSVIMO including extension phases, 3.6% (16/443) of patients receiving SUSVIMO reported conjunctival erosion and 1.6% (7/443) of patients receiving SUSVIMO reported conjunctival retraction in the study eye.

Appropriate intraoperative handling of conjunctiva and Tenon's capsule to preserve tissue integrity and secure closure of peritomy while ensuring placement of sutures away from implant edge may reduce the risk of conjunctival erosion or retraction. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion.

### 5.6 Conjunctival Bleb

A conjunctival bleb is an encapsulated elevation of the conjunctiva above the implant flange, which may be secondary to subconjunctival thickening or fluid. Conjunctival blebs may require surgical management to avoid further complications, especially if the implant septum is no longer identifiable due to the conjunctival bleb.

In clinical trials of SUSVIMO including extension phases, 5.9% (26/443) of patients receiving SUSVIMO reported conjunctival bleb/conjunctival filtering bleb leak in the study eye. Strict adherence to the scleral incision length, appropriate intraoperative handling of conjunctiva and Tenon's capsule to preserve tissue integrity and secure closure of peritomy, and proper seating of the refill needle during refill-exchange procedures may reduce the risk of conjunctival bleb.

### 5.7 Postoperative Decrease in Visual Acuity

Visual acuity was decreased by 4 letters on average in the first postoperative month and 2 letters on average in the second postoperative month following initial implantation of SUSVIMO [*see Clinical studies (14)*].

### 5.8 Air Bubbles Causing Improper Filling of the Implant

Minimize air bubbles within the implant reservoir as they may cause slower drug release. During the initial fill procedure, if an air bubble is present, it must be no larger than 1/3 of the widest diameter of the implant. If excess air is observed after initial fill, **do not** use the implant. During the refill-exchange procedure, if excess air is present in the syringe and needle **do not** use the syringe and needle. If excess air bubbles are observed after the refill-exchange procedure, consider repeating the refill-exchange procedure.

### 5.9 Deflection of the Implant

Use caution when performing ophthalmic procedures that may cause deflection of the implant and subsequent injury. For example, B-scan ophthalmic ultrasound, scleral depression, or gonioscopy.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis *[see Warnings and Precautions (5.1)]*
- Rhegmatogenous Retinal Detachment *[see Warnings and Precautions (5.2)]*
- Implant Dislocation *[see Warnings and Precautions (5.3)]*
- Vitreous Hemorrhage *[see Warnings and Precautions (5.4)]*
- Conjunctival Erosion or Retraction *[see Warnings and Precautions (5.5)]*
- Conjunctival Bleb *[see Warnings and Precautions (5.6)]*
- Postoperative Decrease in Visual Acuity *[see Warnings and Precautions (5.7)]*

### 6.1 Clinical Trials 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 (Table 2) reflect exposure of 248 patients with nAMD in the Archway study following the SUSVIMO initial fill and implant insertion, refill, and implant removal (if necessary) procedures up to Week 40. In this patient population the most common (≥ 10%) adverse reactions up to Week 40 were conjunctival hemorrhage (72%), conjunctival hyperemia (26%), iritis (23%), and eye pain (10%).

**Table 2 Adverse Reactions in nAMD patients occurring in ≥ 4% of patients in the SUSVIMO arm**

| | Week 40 | |
|---|---|---|
| **Adverse Reactions** | **SUSVIMO n = 248** | **Intravitreal ranibizumab n = 167** |
| Conjunctival hemorrhage | 72% | 6% |
| Conjunctival hyperemia | 26% | 2% |
| Iritis[1] | 23% | 0.6% |
| Eye pain | 10% | 5% |
| Vitreous floaters | 9% | 2% |
| Conjunctival bleb/ filtering bleb leak[2] | 9% | 0 |
| Foreign body sensation in eyes | 7% | 1% |
| Headache[3] | 7% | 2% |
| Hypotony of eye | 6% | 0 |
| Vitreous detachment | 6% | 5% |
| Vitreous hemorrhage | 5% | 2% |
| Conjunctival edema | 5% | 0 |
| Corneal disorder | 4% | 0 |
| Corneal abrasion[4] | 4% | 0.6% |
| Corneal edema | 4% | 0 |

[1]Iritis includes: iritis, anterior chamber flare, and anterior chamber cell

[2]Conjunctival bleb/filtering bleb leak includes: conjunctival bleb, conjunctival filtering bleb leak, conjunctival cyst, subconjunctival cyst, and implant site cyst

[3]Headache includes: headache and procedural headache

[4]Corneal abrasion includes: corneal abrasion and vital dye staining cornea present.

### 6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immune response in patients treated with ranibizumab including SUSVIMO. The detection of an immune response is highly dependent on the sensitivity, specificity, and drug tolerance level of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the study described below with the incidence of antibodies in other studies or to other products may be misleading.

In previously treated nAMD patients, anti-ranibizumab antibodies were detected in 2.1% (5 of 243) of patients prior to insertion of the SUSVIMO implant. After the SUSVIMO implant insertion and treatment, anti-ranibizumab antibodies developed in 12% (29 of 247) patients. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety in patients with treatment-emergent anti-ranibizumab antibodies were observed.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SUSVIMO (ranibizumab injection) 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 up to 41 times the human exposure (based on serum levels following the recommended clinical dose). No skeletal abnormalities were observed at serum trough levels similar to the 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)]*, treatment with SUSVIMO (ranibizumab injection) may pose a risk to human embryofetal development.

All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% – 4% and of miscarriage is 15% – 20% of clinically recognized pregnancies.

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 41 times higher than observed human $C_{max}$ levels of SUSVIMO (ranibizumab injection) after treatment of a single eye.

No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures similar to single eye treatment with SUSVIMO (ranibizumab injection) 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 SUSVIMO is administered to a nursing woman.

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

### 8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential should use effective contraception during treatment with SUSVIMO (ranibizumab injection) and for at least 12 months after the last dose of SUSVIMO (ranibizumab injection).

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 SUSVIMO (ranibizumab injection) may pose a risk to reproductive capacity.

### 8.4 Pediatric Use

The safety and efficacy of SUSVIMO (ranibizumab injection) in pediatric patients have not been established.

### 8.5 Geriatric Use

In the Archway study, 90% (222 of 248) of the patients randomized to treatment with SUSVIMO were ≥ 65 years old and approximately 57% (141 of 248) were ≥ 75 years old. No notable difference in treatment effect or safety was seen with increasing age.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients on the following after the implant insertion procedure:

Positioning:

- Keep head above shoulder level for the rest of the day.
- Sleep with head on 3 or more pillows during the day and the night after surgery.

How to care for the treated eye after the procedure:

- Do not remove the eye shield until they are instructed to do so by their healthcare provider. At bedtime, continue to wear the eye shield for at least 7 nights following the implant surgery.
- Administer all post-operative eye medications as directed by their healthcare provider.
- Do not push on the eye, rub the eye, or touch the area of the eye where the implant is located (underneath the eyelid in the upper and outer part of the eye) for 30 days following the implant insertion.
- Do not participate in strenuous activities until 1-month after the implant insertion or after discussion with their healthcare provider.

Magnetic Resonance (MR) Conditional information:

- The SUSVIMO implant is MR conditional. Inform their healthcare provider that they have SUSVIMO implanted in their eye and show their healthcare provider the SUSVIMO implant card should they require Magnetic resonance imaging (MRI).

Advise patients on the following after the Refill-Exchange procedure:

- Refrain from pushing on the treated eye, rubbing the eye, or touching the eye in the area of the implant (located underneath the eyelid in the upper and outer part of your eye) for 7 days following the refill-exchange procedure.
- Administer eye drops as directed by their healthcare provider.

Advise patients on the following after the implant removal procedure (if it is deemed medically necessary):

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head on 3 or more pillows if lying down during the day and the night after implant removal.
- Wear an eye shield for at least 7 nights following the implant removal.
- Do not participate in strenuous activities until 14 days following the implant removal.
- Administer all post-operative anti-inflammatory and antimicrobial drops, as directed by your healthcare provider.

Advise patients on the following throughout SUSVIMO treatment:

- Do not drive or use machinery until the eye shield can be removed and visual function has recovered sufficiently *[see Adverse Reactions (6.1)]*.
- The SUSVIMO implant and/or implant related procedures have been associated with conjunctival reactions (bleb, erosion, retraction), vitreous hemorrhage, endophthalmitis, rhegmatogenous retinal detachment, the dislocation of the implant, and a temporary decrease in vision.
- While the implant is in the eye, avoid rubbing the eye or touching the area as much as possible. However, if necessary to do so, make sure hands are cleaned prior to touching the eye.
- Seek immediate care from an ophthalmologist if there are sudden changes in their vision (an increase in moving spots, the appearance of "spider webs", flashing lights, or a loss in vision), increasing eye pain, progressive vision loss, sensitivity to light, redness in the white of the eye, a sudden sensation that something is in their eye, or eye discharge or watering *[see Warnings and Precautions (5)]*.

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# Surgical Considerations For Vitreous Opacities

## With today's advanced instrumentation and safety profiles, going to the OR is a viable option for the right patient.

**BY MATTHEW A. CUNNINGHAM, MD, AND JAYA B. KUMAR, MD**

Vitreous opacities (VOs), or floaters, are a common finding usually related to a posterior vitreous detachment (PVD). For the vast majority of patients, VOs are bothersome but do not significantly affect their quality of life or activities of daily living. However, when they *do* become visually significant, pars plana vitrectomy (PPV) may be a viable treatment option. This surgical approach was initially discussed more than 20 years ago, but additional evidence now suggests that PPV for the treatment of visually significant VOs is effective and generally safe.[1]

As vitrectomy technology evolves and becomes safer and better tolerated, an increasing number of vitreoretinal surgeons are beginning to offer PPV for patients with symptomatic VOs. In fact, results from a global online survey showed that the majority of respondants believe that symptomatic VOs are a condition that warrants treatment, and this was consistent across geographical regions.[2]

The surgical intervention itself is often straightforward; the real challenge is careful patient selection and extensive patient education.

## HOW TO SELECT THE RIGHT PATIENT

Before you recommend PPV as a treatment option for a patient complaining of floaters, consider these five factors.

### Duration of Symptoms

When addressing a patient bothered by VOs, you should first determine the duration of symptoms. Often, when patients initially develop an acute PVD, they tend to be symptomatic with photopsias and floaters. For most patients, these symptoms will resolve within 3 to 6 months, obviating the need for any further intervention. Within this timeframe, most patients simply need reassurance that their symptoms should resolve on their own.

If a patient with visually significant VOs remains symptomatic after 6 months, we believe it is reasonable to offer vitrectomy.

### Informed Consent

Going over a detailed informed consent process with these patients is extremely important. This patient population typically presents with excellent vision and an unremarkable posterior segment examination. Patients need to understand that even though the vitrectomy surgery may be brief, there

## AT A GLANCE

- Symptoms of photopsias and floaters after a posterior vitreous detachment often resolve within 3 to 6 months, obviating the need for any further intervention in most patients.
- Significant visual opacities are common findings in other conditions, such as intermediate uveitis, ocular amyloidosis, and intraocular lymphoma.
- Spending time with patients to ensure you have the appropriate surgical candidate for vitrectomy and taking into account the various surgical pearls can yield an excellent surgical outcome.

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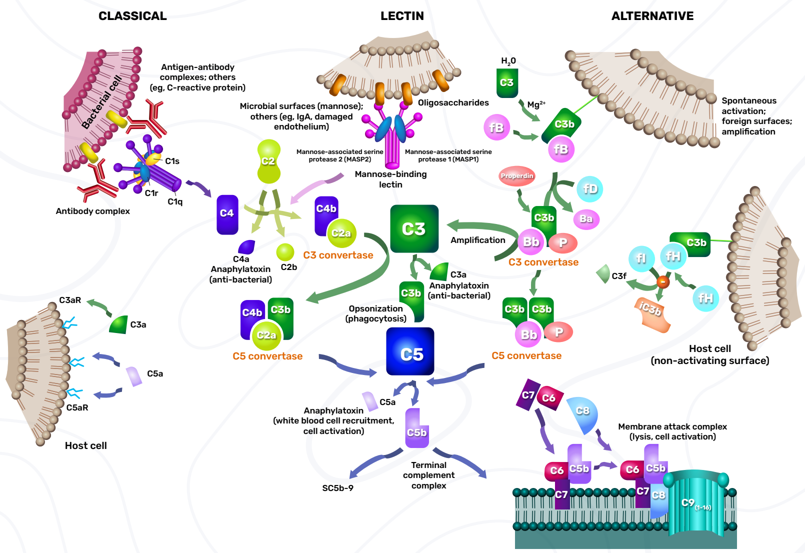
# THE COMPLEMENT CASCADE: A DETAILED REVIEW

BY CHARLES C. WYKOFF, MD, PHD
AND NAMRATA SAROJ, OD




The complement cascade has been implicated in the development of age-related macular degeneration (AMD) and may serve as an effective therapeutic target in patients with geographic atrophy (GA). Many retina specialists have not thought deeply about the complement pathway since their formal medical school education—and for good reason, given the specialized nature of their field, high patient and surgical volumes, and the irrelevance of the complement cascade in day-to-day practice.

However, therapies in the AMD pipeline targeting the complement system have renewed the need for retina specialists to understand how this element of the innate immune system affects the genesis and progression of AMD.

The complement system's elegance is also its complexity, and diving into the overall system without a foundational understanding of the scheme may lead to information overload. With that in mind, it may be wise to remember the four major tenets of the complement system: activation of the complement system, C3 convertase function, C5 convertase function, and formation of membrane attack complex. Building an education of the complement system from those four points will facilitate reorientation with this biologic pathway.

There have been multiple shots on goal when it comes to developing a therapy for GA, and dozens of companies are racing toward finding a target in the complement cascade that could yield a safe and effective treatment. Although numerous clinical trials in GA have yet to yield a therapy that has been approved by the US FDA, savvy retina specialists have noted that data from these studies have helped focus and refine investigations that came after them.

This is not a winner-take-all competition akin to the Space Race of the middle 20th century, but rather a community effort to build a robust set of treatment options for patients who have heretofore been unable to receive therapy. To that end, we invite readers to use any of the illustrated assets in this piece for their own educational purposes. Borrow them for your podium presentations, for your weekly rounds, for teaching trainees—and do so in the spirit of specialty-wide collaboration so that we may further education in the field. You can access a full list of citations as well as the digital assets described above by visiting retinatoday.com/explore-the-complement-system. ■

**CHARLES C. WYKOFF, MD, PHD**
- Director of Research, Retina Consultants of Texas/Retina Consultants of America, Houston
- Deputy Chair for Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston
- ccwmd@retinaconsultantstexas.com
- Financial disclosure: Research Grants and Scientific Advisor (Apellis, Gyroscope, Iveric Bio, NGM)

**NAMRATA SAROJ, OD**
- Principal, All Eyes Consulting, New York
- Namrata.saroj@gmail.com
- Financial disclosure: Consultant (Apellis, Annexon, Gemini)

are inherent risks to every surgery that they must be willing to accept prior to proceeding with surgery.

Discuss these risks (including the possibility of retinal tears/detachment, bleeding, infection, etc.) with the patient, and be sure to document the conversation.

## Lenticular Status

Although many reports have involved phakic patients over the years, we recommend a patient be pseudophakic prior to undergoing vitrectomy for symptomatic VOs. Performing surgery in a phakic patient can often result in an incomplete vitrectomy, with residual vitreous remaining posterior to the lens capsule. This residual vitreous can cause postoperative visual disturbances in patients. However, when the patient is pseudophakic, the surgeon can place the vitrector directly posterior to the IOL and clear any anterior vitreous present.

## PVD Status

Ensure the presence of a PVD prior to considering vitrectomy to avoid inducing a PVD intraoperatively; this can result in iatrogenic retinal breaks, retinal detachment (RD), or hemorrhage.[3] A PVD can often be confirmed clinically by the presence of a Weiss ring. Various imaging modalities, such as B-scan ultrasonography and OCT, can also help you to confirm a PVD.

If a PVD is not present and you decide to proceed with vitrectomy, counsel the patient that symptoms may reoccur if a PVD develops in the future.

## Mimickers

It is important to remember that not all VOs are due to a PVD or vitreous syneresis. Significant VOs are common findings in other conditions, such as intermediate uveitis,[4] ocular amyloidosis,[5] and intraocular lymphoma (Figure).[6]

While these conditions may also require a PPV, tissue biopsy or pathological analysis is critical to confirm the correct diagnosis. Additionally, in the case of VOs secondary to uveitis, treating with ocular steroids will improve the VOs and other symptoms; therefore, it is important to consider all possible etiologies of a patient's VOs prior to discussing and rushing to vitrectomy surgery.

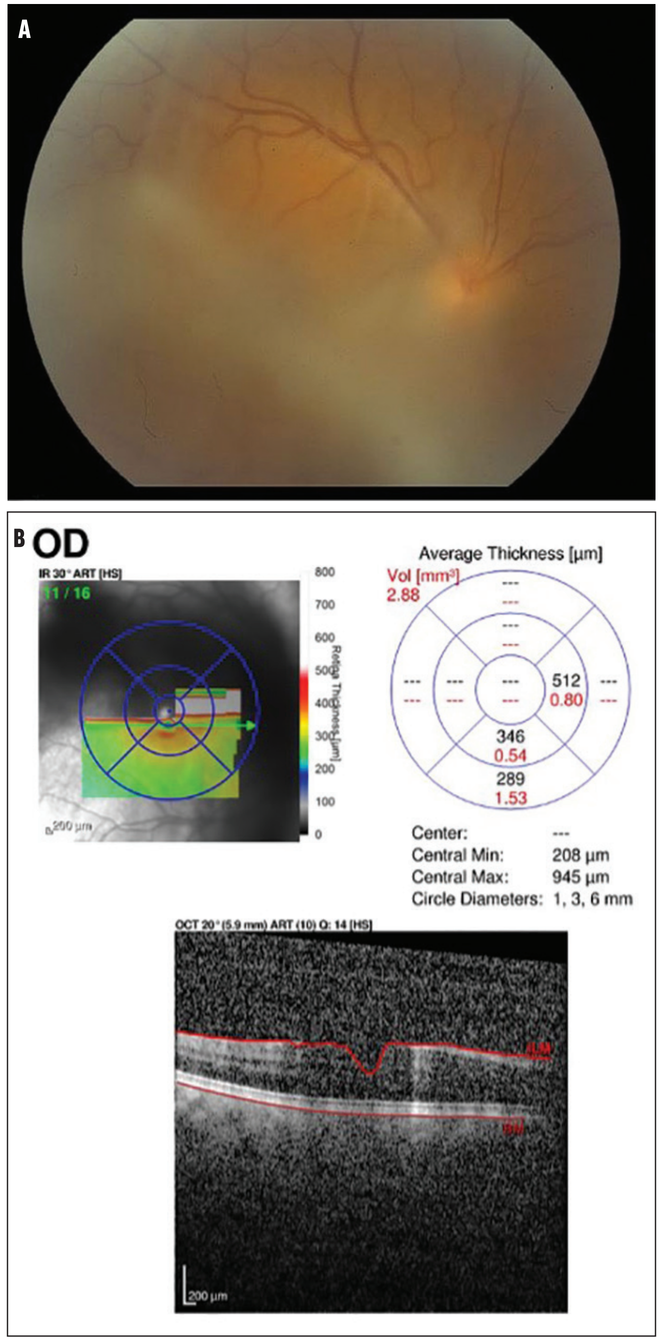



Figure. This 40-year-old man presented with bilateral, visually significant VOs (A). The corresponding OCT image and scanning laser ophthalmoscope confirm the significant VOs (B). He underwent PPV, and the vitreous was sent for pathologic analysis. Based on the results, he was diagnosed with ocular amyloidosis.

## SURGICAL PEARLS

Once you have decided that a patient with symptoms for at least 6 months is ready, discuss the possibility of PPV as a treatment option to remove their symptomatic VOs. You should schedule the patient only after a thorough informed consent and discussion of all the risks, benefits, and alternatives to surgery. Once you are in the OR, these surgical pearls can help ensure the surgery goes smoothly.

- We recommend small-gauge vitrectomy platforms. A study evaluating 110 vitrectomies for vitreous floaters found a high rate of postoperative RD (11%), and more than 50% of those with an RD underwent 20-gauge PPV.[7] Smaller-gauge vitrectomy has been found to be safer, more efficient, and better tolerated by patients.[8-10]
- After performing a core vitrectomy, use the vitrectomy cutter to clear the vitreous posterior to the IOL. This will prevent any mild visual disturbances postoperatively.

**WHILE THE GENERAL APPROACH HAS BEEN TO SIMPLY EDUCATE PATIENTS THAT VITREOUS FLOATERS ARE A BENIGN CONDITION WITH NO LONG-TERM SEQUELAE, MANY INDIVIDUALS AFFECTED WITH SIGNIFICANT VISUAL OPACITIES FIND THEM DEBILITATING TO THEIR QUALITY OF LIFE.**

- If the patient has not already undergone a YAG capsulotomy, consider performing a posterior capsulotomy with the cutter. If patients develop capsular opacification in the future and require a YAG capsulotomy postvitrectomy, the procedure would cause a new vitreous opacity that may result in recurrence of symptoms.
- Perform a thorough scleral depressed examination to check for any suspicious areas in the periphery (ie, tufts, small retinal breaks, lattice with atrophic holes). Have a very low threshold to perform barricade laser around any concerning areas in the periphery.
- Performing a partial or full air-fluid exchange can assist in ensuring the sclerotomies are closed after the cannulae are removed. If there is any leakage of air through a sclerotomy site, have a low threshold to suture.

## NEW DATA

We recently published our experience of PPV for visually significant VOs at a retina-only private practice over a 4-year period. Patients underwent either a 23- or 25-gauge PPV. All patients included in the study were pseudophakic, had symptoms for more than 6 months, and had a Weiss ring present; abiding by this criteria, we enrolled 81 patients (104 eyes). We had no cases of retinal tears or RDs in our series. One patient developed a vitreous hemorrhage, which resolved spontaneously.[11] Additionally, all of the patients had improved visual acuity, 93.3% of whom achieved a VA of 20/40 or better.

While the general approach has been to simply educate patients that vitreous floaters are a benign condition with no long-term sequelae, many individuals affected with significant VOs find them debilitating to their quality of life.

Recently, Donald J. D'Amico, MD, led a panel of vitreoretinal experts who addressed the management of symptomatic VO cases. The panel proposed a VO severity grading system, which could be a good resource for optometrists and ophthalmologists to monitor patients who complain of VOs.[2] The group came to a consensus on these definitions:

- **Asymptomatic VOs:** noticeable on clinical examination but cause no visual disturbances to the patient.
- **Mild VOs:** noticeable to the patient but do not interfere with vision or functions of daily living.
- **Moderate VOs:** impact vision and interfere somewhat with functions of daily living.
- **Severe VOs:** highly impact quality of life and significantly interfere with functions of daily living.

Spending time with patients to ensure you have the appropriate surgical candidate for PPV and taking into account the various surgical pearls can yield an excellent surgical outcome and improved patient satisfaction. ■

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**MATTHEW A. CUNNINGHAM, MD**
- Vitreoretinal Surgeon, Research Director, Florida Retina Institute, Orlando, Florida
- mcunningham@floridaretinainstitute.com
- Financial disclosure: Consultant (Alimera, Allergan, Novartis)

**JAYA B. KUMAR, MD**
- Vitreoretinal Surgeon, Partner, Florida Retina Institute, Orlando, Florida
- jayak@floridaretinainstitute.com
- Financial disclosures: Consultant (Alimera)


SET IT!
AND FORGET IT!

# Today's Perspective on Proliferative Vitreoretinopathy






This complication continues to plague retina surgery, but new techniques and treatments are helping to reduce its incidence.

A DISCUSSION WITH DEAN ELIOTT, MD; AVNI P. FINN, MD, MBA; AJAY E. KURIYAN, MD, MS; AND M. ALI KHAN, MD
MODERATED BY ALLEN C. HO, MD, AND ROBERT L. AVERY, MD

*Our patients remind us of significant opportunities for improvement of retinal detachment (RD) repair—for example, poor vision despite anatomic retina reattachment and the need for repeat RD surgery most commonly due to proliferative vitreoretinopathy (PVR). Perhaps neuroprotective agents in early clinical trials will improve visual outcomes via photoreceptor protection from cell death pathways activated by detachment. There is a long history of failed agents for PVR prevention after RD repair, but there may be hope on the horizon. With improved tools and techniques, we are better at addressing PVR surgically, but we must find ways to attack this problem systematically. We sat down with colleagues to discuss the recent research and latest surgical techniques for tackling PVR in the OR.*

**- Allen C. Ho, MD, and Robert L. Avery, MD**

## ALLEN C. HO, MD: WHAT ARE SOME MAJOR KNOWLEDGE GAPS REGARDING PVR DEVELOPMENT?

**M. Ali Khan, MD:** Generally, we have conceptualized PVR as a cytokine-driven process in the vitreous that allows for the abnormal proliferation of retinal pigment epithelium (RPE) cells, leading to clinical PVR. Many molecular targets have been identified to inhibit that cytokine-driven cascade, but no specific agent has proven effective at treating or preventing PVR to date.

We don't fully understand the pathophysiology, and it's likely more complex than we have simplified. We have animal models of PVR, but we do not know how accurate those models are in predicting human disease. Studying the disease in humans is difficult, and there hasn't been many powered clinical trials evaluating therapeutics for PVR. Hopefully, some current trials will fill in some gaps and encourage larger studies.

## AT A GLANCE

- Certain patient factors can increase the risk of proliferative vitreoretinopathy (PVR), including younger age, ocular trauma history, and smoking.
- Many are hoping the GUARD trial evaluating intravitreal methotrexate will be successful, as it would be a promising, local treatment for patients with established PVR.
- One of the potential reasons for PVR, even with today's advanced techniques, is that surgeons are leaving a residual layer of anterior or posterior cortical vitreous that they don't recognize.

### ROBERT L. AVERY, MD: WHAT ARE THE OCULAR AND SURGICAL RISK FACTORS FOR PVR?

**Avni P. Finn, MD, MBA:** Certain patient factors can increase the risk of PVR and redetachment, including younger age, a history of ocular trauma, and smoking. As for clinical history, a patient with a history of chronic RD or vision loss for a longer period may be at an increased risk for PVR, which takes about 4 to 6 weeks to develop.

During the preoperative examination, it is important to note any vitreous hemorrhage, giant retinal tears, choroidal detachments, hypotony, or uveitis, all of which predispose a patient to PVR or redetachment.

When I see any of these, I counsel my patients about the fact that they may be at a higher risk for scar tissue forming (that's the word I use when I talk about PVR) and that they may be at heightened risk for a redetachment as well.

### DR. HO: WHAT'S THE PERCENTAGE YOU QUOTE THAT THERE'S A CHANCE OF PVR AND/OR REDETACHMENT?

**Dr. Finn:** I usually tell patients that 90% of the time RDs are fixed with the first surgery, and that's variable across surgeons. That's a reasonable number that falls within the data from large retrospective series for primary RDs.

**Dr. Ho:** I tend to be a little more conservative and usually say 85%. In that, I am including anything that would require a second surgery.

**Dr. Avery:** I usually tell patients 95%, because we reviewed nearly 1,000 of our cases, and we had close to a 97% success rate with vitrectomy or scleral buckle/vitrectomy surgery when we excluded cases with preexisting PVR. Of course, if a patient is at high risk for PVR, I reduce that dramatically.

**Dean Eliott, MD:** I tell patients roughly 90%, and I may tweak it by saying, "You have a straightforward RD with one small retinal break, and your odds are probably a bit better than that." I worry that if you say 95% or 97%, the patient assumes it won't happen to them, which may defeat the purpose of telling them that there's a probability of failure.

**Dr. Khan:** Patients can understand that they have a one in 10 chance of failure. If they have high-risk features, you need to set them up to understand that the opportunity exists for PVR to develop. Patients who are told that there's a chance of it beforehand aren't so disappointed if it happens. But patients who are never told there was a chance of failure are really upset about what happened during the surgery.

### DR. HO: WHAT ARE SOME OF THE THINGS WE CAN DO, PHARMACOLOGICALLY, TO MODIFY THE RISK OF PVR?

**Ajay Kuriyan, MD, MS:** We are excited to have an ongoing trial investigating the use of intravitreal methotrexate (Aldeyra Therapeutics), and we are eager for the results.[1] It certainly looks promising, based on my experience with it through the study.

Other than that, we don't have anything to treat patients who already have PVR. Dr. Khan is working on a study investigating the use of anti-VEGF agents, which target the non-canonical platelet-derived growth factor pathway, to prevent PVR.[2] That approach may allow us to identify patients who are at a high risk for developing PVR and prevent it from happening.

Dr. Eliott also did some great work to identify smoking as a risk factor for PVR formation.[3] We don't quite know if smoking cessation at the time of repair modifies your risk for developing PVR later, but I always use it as a great opportunity to do smoking cessation counseling.

## SIDELINED THERAPEUTICS

Many trials have been conducted to try to inhibit proliferative vitreoretinopathy, none of which have succeeded so far.

- Broad antiinflammatory agents such as the dexamethasone implant, triamcinolone, and systemic prednisone
- Antiproliferative agents (liposome-encapsulated 5-fluorouracil, colchicine, daunorubicin, low molecular weight heparin, retinoic acid, and ribozyme-proliferating cell nuclear antigen)
- Anti-VEGF agents for patients with PVR

### DR. AVERY: THE METHOTREXATE TRIAL INCLUDES 13 TREATMENTS INSTEAD OF 10, WHICH WAS THE CASE 5 YEARS AGO. WHY THE CHANGE AND THE NEED FOR PROTRACTED INTERVENTION?

**Dr. Eliott:** In the phase 1 study, we gave one injection of methotrexate at the end of surgery, eight weekly injections, and one more at week 12. One of the patients in the study had a 13 mm open-globe injury and developed a total RD with retinal incarceration in the scleral wound. We repaired the RD with retinectomy and oil and followed the study protocol using 10 methotrexate injections. At 12 weeks the patient looked good, but at the 16-week visit, he had a massive amount of pigment cells in the oil, a striking difference from 4 weeks prior. Soon thereafter he developed explosive PVR and ended up with light perception visual acuity.

Usually, PVR develops in a month or two following an open-globe injury, and it was unusual for this patient to have no evidence of PVR for 3 months (during the injection period), and then to suddenly develop severe PVR at 4 months. This patient must have had a very high stimulus for PVR development, so we thought that increasing the number of injections to extend the treatment period might be beneficial in some patients. The GUARD study includes 13 injections, which may be overkill in many patients (assuming the drug proves useful for the treatment of PVR).[1]

## DR. AVERY: AS FOR THE SURGERY ITSELF, ARE THERE ANY MANEUVERS THAT HELP TO PREVENT HYPOTONY, ONE OF THE PROBLEMS WITH PVR?

**Dr. Finn:** No PVR surgery is ever easy, and you can't approach all of them with the same methodology. But, among the first things I consider is putting a buckle on an eye with severe PVR if there's not already one present and I'm not planning on doing a 360° retinectomy. I also consider visualization during the case. If there is a cataract, I perform a lensectomy because you always need an excellent view to address the PVR.

When it comes to the vitrectomy, we all know that an incompletely removed hyaloid can lead to PVR and membrane formation; thus, it is important to stain and make sure that you are peeling posterior membranes that have grown on the scaffold of the posterior hyaloid.

I use perfluoro-n-octane to start stabilizing and flattening the retina after I've removed those posterior membranes, then I make my way out more peripherally. The MaxGrip forceps (Alcon) and a lighted pick are my go-to instruments. When I don't have an assistant, I use a chandelier so that I can use a bimanual technique.

When you're finishing up the case, especially if you've performed a retinectomy, good hemostasis is crucial to prevent further PVR and redetachment because hemorrhage can be a problem. In these cases, I also choose a long-acting tamponade such as $C_3F_8$ gas or silicone oil.

## DR. AVERY: WHEN SHOULD WE USE A SCLERAL BUCKLE IN THE ABSENCE OF THE 360° RETINECTOMY?

**Dr. Eliott:** I like to have a buckle in PVR cases. There are two instances when I wouldn't put one on: when I perform a 360° retinectomy, and when the patient has had prior extensive 360° peripheral laser.

But in other cases, I believe that a buckle helps. I know it is controversial, and I may not be right, but I err on the side of doing too much rather than too little. I like to use a buckle even when I have a 180° inferior retinectomy.

**Dr. Khan:** It's probably 50/50 for me. With many cases of 180° retinectomy, I don't put on a buckle. There are surgeon-specific factors, and everybody figures out what works best in their own hands and experience. We don't have great evidence that adding a buckle really affects the outcomes. That's partially why PVR is so frustrating because it doesn't always make sense.

But I stain with ICG, especially if the PVR is more posterior, and try to peel from the internal limiting membrane and the macula as far out as I can.

**Dr. Ho:** We do more retinectomies now, and although we may not have good data on it, the surgeons in our department know that you must do a significant retinectomy if you're going to do an inferior retinectomy at all. You should think twice about doing a retinectomy less than 120°, because it is going to fail.

When you go more than 120°, and typically I'm at 180° or greater for a bad case, the need for a buckle is obviated. I do a lot of scleral buckles on RD surgery, but when you start, just like in a giant retinal tear, I don't see the sense of putting a scleral buckle on a lot of those cases.

One of the main reasons for PVR, even with today's advanced techniques, is that we're leaving a residual layer of anterior and posterior cortical vitreous that we don't recognize. I perform vitreous base shaving, which includes depression with particles like triamcinolone to identify that layer. You must take the time to remove the gel that straddles the pars plana and ora serrata that will contract either with gas compression or silicone oil and lead to anterior loop proliferation. Also, removing that posterior gel may be helpful to reduce the incidence of PVR, and we need data on this clinical impression.

**Dr. Eliott:** For PVR surgery, in my opinion, you should be more of a maximalist than you are with other diseases such as retinopathy of prematurity, where it's better to be a minimalist (so you don't make a retinal break). In PVR cases, I like to remove everything—vitreous and membranes—as much as possible.

## DR. HO: WHAT ARE YOU MOST EXCITED ABOUT FOR THE TREATMENT OR PREVENTION OF PVR?

**Dr. Khan:** I think many are hoping the GUARD trial evaluating intravitreal methotrexate will be successful, as it would be a promising, local treatment for patients with established PVR.[1] Isotretinoin has had promising data in prior studies, but it is difficult to prescribe with many potential systemic side effects.

I'm also interested in homing in on what is characterized as a 'high-risk' eye to better understand which primary RDs may be the best candidates for preventative treatment options. We need clinical trials on high-risk primary RDs, not just patients with advanced, grade C PVR.

It's going to take a lot of people working on this together because doing prospective clinical trials alone is difficult and doing it in surgery is even harder.

**Dr. Kuriyan:** Methotrexate is the closest option we may have, but there's a lot of exciting preclinical work for other agents. Leo A. Kim, MD, PhD, at Massachusetts Eye and Ear in Boston, has done some great work looking at runt-related transcription factor 1 inhibitors and working toward a study of rho-kinase inhibition, both of which are exciting.[4,5]

We have some work in our lab looking at soluble amniotic membrane and a compound with salinomycin, which has been found to reverse some of the scar phenotype.[6-8]

ALEXION
AstraZeneca Rare Disease

## DR. HO: WHAT'S THE LATEST WITH THE GUARD TRIAL?

**Dr. Eliott:** The GUARD trial's goal was to enroll up to 100 patients, and at first patients were randomly assigned to either standard-of-care, which is surgery alone, or standard-of-care with methotrexate. At some point the protocol was altered to put all patients into the standard-of-care surgery plus methotrexate arm. Enrollment should be completed soon, and then we'll be able to evaluate the effect.

Keep in mind that the power to detect a difference in this study is relatively low due to the small number of patients. As with all surgical studies, it faces some difficulties with surgeon variability. It is very difficult to do a surgical study and ensure that all variables are the same except for the drug. Nevertheless, we will get some answer whether there's a signal that the drug might work.

It's an exciting time, but there are some challenges ahead.

## DR. HO: ANY FINAL THOUGHTS ON WHERE WE STAND WITH PVR?

**Dr. Finn:** Rare surgical diseases, like PVR, don't get as much attention as more common medical diseases such as AMD and diabetic retinopathy. We are looking at a very small percentage of our overall patient population, but it is something that haunts all of us as surgeons. I'm excited to be on the precipice of, hopefully, new discoveries in terms of the pathophysiology, and also potential adjuncts outside of surgery to add to our toolbox.

**Dr. Khan:** We have a lot of preclinical work and active clinical trials, and we need to continue to evaluate our own surgical techniques to see if there's something iatrogenic that could be worsening PVR. I think for a while we as a retina community lost interest in PVR because nothing was working, but the interest is certainly back. Hopefully the momentum keeps going.

**Dr. Kuriyan:** With all of the advancements in genetic and single-cell analyses, we can revisit older studies that weren't fruitful to better understand the pathophysiology and then work toward developing more pharmacologic agents.

**Dr. Avery:** It's nice to finally be bringing pharmacotherapy to this important topic. This is an exciting topic now because of these advances, and I want to thank you all for sharing your expertise with us today. ■

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**ROBERT L. AVERY, MD**
- Founder and CEO, California Retina Consultants, Santa Barbara, California
- Associate Medical Editor, *Retina Today*
- bobave@gmail.com
- Financial disclosure: Consultant (Adverum, Allergan, Amgen, Apellis, Asclepix, Eyepoint, Clearside, Genentech/Roche, Novartis, Ocular Therapeutix, Regenxbio, Revana); Equity (Adverum, Aldeyra, Eyepoint, Kodiak, Novartis, Regeneron, Revana)

**DEAN ELIOTT, MD**
- Director, Retina Service, Massachusetts Eye and Ear, Boston
- Stelios Evangelos Gragoudas Professor, Harvard Medical School, Boston
- Editorial Advisory Board Member, *Retina Today*
- Dean_eliott@meei.harvard.edu
- Financial disclosure: Consultant (Alcon, Alderya Therapeutics, Asclepix, Dutch Ophthalmic, Glaukos); Scientific Advisory Board (Pykus Therapeutics); Stockholder/Royalties (Aldeyra)

**AVNI P. FINN, MD, MBA**
- Assistant Professor, Department of Ophthalmology and Visual Sciences, Vanderbilt University Medical Center, Nashville, Tennessee
- avni.finn@vumc.org
- Financial disclosure: Advisory Board (Allergan, Genentech/Roche); Consultant (Apellis); Honorarium (Allergan, Genentech/Roche)

**ALLEN C. HO, MD**
- Director of Retina Research, Wills Eye Hospital, Philadelphia
- Professor of Ophthalmology, Sidney Kimmel Medical College and Thomas Jefferson University, Philadelphia
- Chief Medical Editor, *Retina Today*
- achomd@gmail.com
- Financial disclosure: Consultant/Grant Funding (Adverum, Apellis, Asclepix, Clearside, Iveric Bio, Genentech/Roche, Gyroscope, Kodiak, Lineage, Regenxbio)

**M. ALI KHAN, MD**
- Retina Service, Wills Eye Hospital, Philadelphia
- Assistant Professor of Ophthalmology, Sidney Kimmel Medical College and Thomas Jefferson University, Philadelphia
- ali.khan.05@gmail.com
- Financial disclosure: Consultant (Allergan, Genentech/Roche, Apellis); Grant Support (Regeneron)

**AJAY E. KURIYAN, MD, MS**
- Retina Service, Wills Eye Hospital, Philadelphia
- Associate Professor of Ophthalmology, Sidney Kimmel Medical College and Thomas Jefferson University, Philadelphia
- ajay.kuriyan@gmail.com
- Financial disclosure: Consultant (Alimera Sciences, Allergan, Bausch Health, Genentech/Roche, Recens Medical, Regeneron, Spark Therapeutics); Grant Funding (Genetech/Roche, Second Sight Medical Products)

# At-Home Monitoring Tools For Today and Tomorrow

**These new technologies could help diagnose retinal conditions early, follow patients between clinical visits, and prevent progression.**

**BY DINAH ZUR, MD; MATIAS IGLICKI, MD, PHD; AND ANAT LOEWENSTEIN, MD, MHA**

AMD and diabetic retinopathy (DR)/diabetic macular edema (DME) are the most frequent causes of blindness in elderly people and working-age adults, respectively, and the incidences continue to rise as life expectancy increases.[1,2]

Although regular ophthalmic examinations are recommended for all patients with diabetes, those with this condition often present for an eye examination only once vision loss has occurred. This lack of proper screening and care is particularly concerning because prompt treatment of DR can prevent blindness in more than 90% of cases when the right treatment is administered following timely diagnosis.[3]

A similar trend plagues the AMD patient population. Early detection of macular neovascularization in patients with AMD is paramount to preserve long-term visual acuity. In real-world conditions, patients start anti-VEGF treatment with a delay of about 2 months from onset of symptoms.[4,5] This lost time often leads to permanent visual impairment.

Early detection of AMD and DR/DME relies on frequent visits to a retina specialist's office for examination and retinal imaging.[6] However, as the COVID-19 pandemic has made abundantly clear, these visits can pose a significant burden on patients and health systems. Added to that, changes that take place between regularly scheduled visits may indicate progression long before the patient presents to the clinic.[7]

The ability to monitor patients at home with objective tools offers a new level of care with the promise of reduced visits, early detection of treatable conditions, acquisition of high-quality patient data, and personalization of treatment regiments. Thus, researchers and clinicians have been exploring at-home tools that can capture ophthalmic data.

## PHONE-BASED TOOLS

A prospective study demonstrated that elderly patients with wet AMD and DME were willing and able to comply with daily self-testing using their mobile device.[8] Thus, several smartphone applications are available or are currently under investigation for at-home vision tests.[9,10] One smartphone application is myVisiontrack (Vital Art and Science/Genentech), which tests shape-discrimination hyperacuity.[11,12] A second application, Alleye (Oculocare Medical), has several similarities with myVisiontrack, but examines a larger central visual field. Both applications are FDA approved for prescription use only.

## AT A GLANCE

- Research shows that prompt treatment of diabetic retinopathy can prevent blindness in more than 90% of cases when the right treatment is administered after a timely diagnosis.
- A prospective study demonstrated that elderly patients with wet AMD and diabetic macular edema are willing and able to comply with daily self-testing using their mobile device.
- Home monitoring may provide clinicians more reliable follow-up to help them provide proper treatment at the proper time.


Image courtesy of Notal Vision

Figure 1. The ForeseeHome monitoring system includes an in-home preferential hyperacuity perimetry device that sends data to a remote monitoring center.

OdySight (Novartis/Tilak Healthcare) is a mobile medical video game, available by prescription only, that contains a puzzle game and a monocular vision test, including near visual acuity, contrast sensitivity, and a digital Amsler grid.[13] The test results are sent via a secure server to an online dashboard that can be accessed online by the physician. Any vision decline triggers alerts sent to both the patient and physician. Results from a prospective study demonstrated good agreement between the near visual acuity and Amsler grid modules of OdySight compared with current standards. The application remains under investigation and might offer additional benefit after implementation of technology to ensure the tests are performed at a standardized distance and with adequate ambient light, as measured by the device.[14]

Online Amsler grids are available for mobile devices (amslerapp.com). Although the Amsler chart has the benefit of being straightforward and easily understood by patients, its usefulness as a monitoring tool is limited by a high false negative rate.

## AT-HOME MEDICAL DEVICES

The preferential hyperacuity perimetry (ForeseeHome, Notal Vision) is an artificial intelligence-enabled device for patient self-testing for AMD.[6] It was designed to detect progression from intermediate to wet AMD. The ForeseeHome is an FDA-approved medical device that uses macular perimetry based on hyperacuity (Figure 1).[15] The randomized controlled Age-Related Eye Disease Study 2-Home Monitoring of the Eye study of the ForeseeHome device showed that early detection of wet AMD resulted in better visual outcomes compared with standard monitoring of wet AMD.[16] The instrument is intended to be used at home for patients with stable fixation and visual acuity of 20/60 or better.

Today, the ForeseeHome AMD Monitoring Program is available by physician referral to the Notal Vision Monitoring Center, a digital health care provider, and covered by Medicare insurance in the United States. It is intended to be used in addition to regular dilated eye examinations in patients with at-risk intermediate AMD. A real-world data analysis showed that the home monitoring system helped to detect wet AMD conversion at a VA of 20/40 or better in 81% of patients.[17]

Image courtesy of Notal Vision

Figure 2. Notal Vision's home OCT device remains under investigation for at-home imaging for patients with AMD.

Exudative maculopathies are mostly managed in two ways: prn or treat-and-extend regimens. Both approaches require regular office visits with OCT imaging to dictate the decision to treat or extend. The ability to monitor the macular status by home OCT represents a novel paradigm of disease monitoring and may allow truly customizable retreatment decisions. The Notal Vision Home OCT system includes an OCT device for patient self-imaging and a dedicated remote monitoring center to support and monitor patient adherence (Figure 2). The system uses a deep learning-based algorithm for automated and quantitative evaluation of the OCT scans, and a telemedicine infrastructure to enable secure transmission and storage of the personal health information.[18]

A prospective pilot study showed that patients with wet AMD were generally able to perform daily self-imaging with the home OCT.[19] The integrated system showed high agreement with human expert grading for the presence and quantity of retinal fluid and permitted detailed characterization of fluid dynamics.

## FINAL THOUGHTS

With today's advances in digital image processing and communications, we strongly believe that these tools can become viable screening options for patients at risk for developing wet AMD, or referrable/vision threatening diabetic eye disease, no matter their location or distance from the clinic.

Smartphone applications and at-home monitoring systems may enable alternative paradigms of disease management.

*(Continued on page 48)*

# Drug Delivery Beyond the Intravitreal Space

Here's what you need to know about the subretinal and suprachoroidal approaches.

BY AARON NAGIEL, MD, PHD

The first intravitreal injection was performed in 1911 by Ohm to repair a retinal detachment using air.[1] The technique became more widespread in subsequent decades as a primary method for intraocular drug delivery in the setting of endophthalmitis. However, it wasn't until the advent of anti-VEGF medications that intravitreal injection became a mainstream technique. It goes without saying that, for most retina specialists, it remains the most common intraocular procedure.

Despite its excellent safety profile, intravitreal delivery of certain medications poses inherent limitations. This has been addressed recently through the development of novel alternative delivery methods—such as suprachoroidal and subretinal—that possess key advantages.

## INTRAVITREAL DELIVERY WOES

Intravitreal drug delivery has three key advantages: (1) it can be done via an inexpensive in-office procedure, (2) it can provide therapeutic levels of medication over weeks to months, and (3) it has an excellent safety profile with endophthalmitis the only major (yet rare) complication.

For the delivery of antibiotics, it is a clear winner, but the need for frequent anti-VEGF injections creates a significant treatment burden for patients. Furthermore, intravitreally delivered steroids or adeno-associated virus (AAV)-based gene therapies may come with serious potential side effects.

Early in the use of intravitreal steroid delivery, it became clear that cataract and elevated IOP were considerations that could limit its use. The SCORE study demonstrated that the 4 mg triamcinolone group had significantly higher rates of cataract surgery and elevated IOP.[2] Although the advent of sustained-delivery steroid formulations may ameliorate some of these concerns, they remain inherent to the side effect profile.[3] For example, the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences) has an incisional glaucoma surgery rate of up to 4.8%.[4]

In a similar fashion, the advent of AAV-based gene therapy has required the development of novel approaches to provide access to the subretinal space for transduction of the photoreceptors or retinal pigment epithelium (RPE) cells. Subretinal delivery is thought to also limit the inflammatory response to the viral vector. In the phase 1/2 trial of intravitreal AAV8-RS1 gene therapy for X-linked retinoschisis, there was a clear dose-dependent trend in anterior and vitreous inflammation.[5] Recently, a case of severe inflammation and hypotony was reported from the INFINITY trial of intravitreal injection of ADVM-022 (Adverum) for diabetic macular edema, resulting in even more scrutiny of intravitreal gene therapy.[6]

## SUBRETINAL DELIVERY

Retinal surgeons are generally familiar with the subretinal delivery of tissue plasminogen activator via a subretinal cannula. This technique is often performed in the setting of large submacular hemorrhages where the subretinal space is accessible. However, even when the retina must be intraoperatively detached for gene therapy delivery, this technique has several advantages, including the use of a three-port vitrectomy.

## AT A GLANCE

- Despite its excellent safety profile, intravitreal delivery of certain retina medications poses inherent limitations.
- When delivering viral vectors, a subretinal approach appears to sequester the vector in the subretinal space with limited egress from the retinotomy.
- Compared with subretinal delivery, suprachoroidal delivery obviates the need for a vitrectomy, the creation of a retinotomy, or the use of air tamponade.

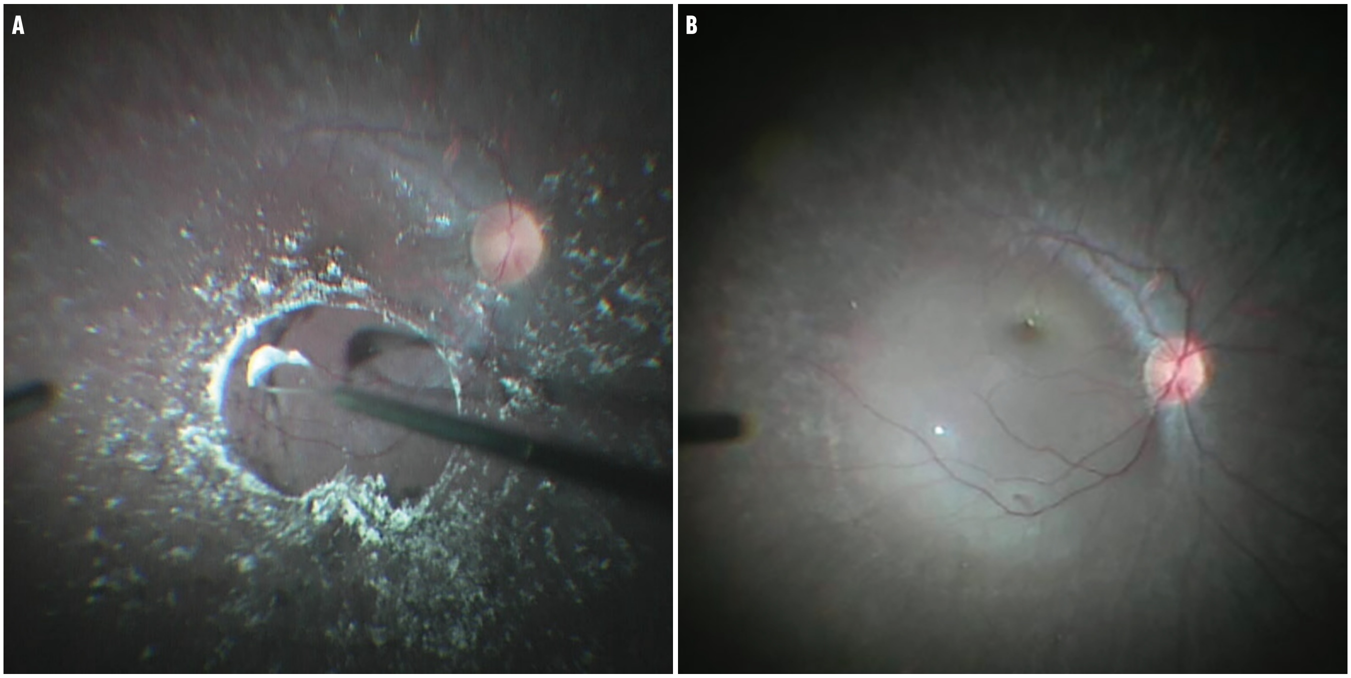


Figure. During subretinal delivery of voretigene neparvovec-rzyl in the left eye of a child, posterior vitreous separation can be aided using a 25-gauge Finesse Flex Loop (Alcon) after staining the cortical vitreous with triamcinolone (A). The 0.3 ml bleb of subretinal voretigene was delivered via a retinotomy along the superior arcade and encompasses most of the macula (B).

Two important surgical steps include (1) the induction of a posterior vitreous separation to avoid any subsequent traction on the retinotomy site and (2) the initiation of the bleb near the arcades using gentle pressure to avoid foveal blowout (Figure). When delivering viral vectors, this approach appears to sequester the vector in the subretinal space with limited egress from the retinotomy, especially when followed by air-fluid exchange. Any vector that leaks into the vitreous cavity can be removed via either extended vitreous washout or air-fluid exchange. Not only does this limit inflammatory sequelae, it may also be the only method capable of efficiently delivering vector to the photoreceptor and RPE cells. Of note, this does not apply to gene therapy for neovascular AMD, where the transduced cells serve as a biofactory for anti-VEGF protein and need not be located in the subretinal space.

## SUPRACHOROIDAL DELIVERY

An attractive alternative to both subretinal and intravitreal drug delivery has been the suprachoroidal approach. Compared with subretinal delivery, suprachoroidal delivery obviates the need for a vitrectomy, the creation of a retinotomy, or the use of air tamponade. Compared with intravitreal injections, the suprachoroidal approach may avoid some of the toxicities relating to exposure of the anterior segment, such as cataract and elevated IOP for steroids and inflammation for viral vectors. In the setting of gene or cell-based therapy, the suprachoroidal approach can even be used to access the subretinal space via a catheter.[7] However, the most straightforward delivery approach is via direct injection using a short (guarded) needle, in a procedure similar to an intravitreal injection.

**IT'S CLEAR THAT THE SUBRETINAL AND SUPRACHOROIDAL APPROACHES HAVE A SOLID FOOTING IN THE VITREORETINAL ARMAMENTARIUM.**

The US FDA's recent approval of the triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb and Clearside Biomedical) for macular edema in noninfectious uveitis has officially put the suprachoroidal drug delivery approach on the map. This approval was based on the results of the phase 3 PEACHTREE study, which randomly assigned 160 patients to suprachoroidal injection of triamcinolone acetonide suspension (CLS-TA) or sham.[8] Strikingly, 47% of the treatment arm experienced a 3-line gain compared with 16% in the sham group, with a corresponding reduction in central foveal thickness.

Other studies are testing its use in the setting of macular edema due to retinal vascular disease. The TANZANITE study has shown promising results with the use of suprachoroidal CLS-TA in combination with intravitreal aflibercept (Eylea, Regeneron) compared with aflibercept alone for the treatment of retinal vein occlusion.[9] These studies use Clearside's proprietary SCS microinjector.

In addition to its obvious advantages for steroid delivery, the suprachoroidal approach may prove useful for gene therapy. Initial efforts used a suprachoroidal catheter to deliver cell therapy via a cannula passed through the suprachoroidal space.[7] Although these early studies were plagued by surgical complications, suprachoroidal delivery remains a creative and attractive possibility for the delivery of AAV-based gene therapies. The focus has shifted toward using the suprachoroidal tissues as biofactories to produce proteins such as anti-VEGF. Regenxbio's phase 2 AAVIATE and ALTITUDE studies have shown promising results with AAV8 encoding an anti-VEGF antibody fragment injected into the suprachoroidal space via the SCS microinjector. The study goals are to generate sustained intraocular anti-VEGF levels and avoid issues affected by subretinal and intravitreal delivery of the vector.

## CONCLUSION

With the approval of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) in 2017 and the triamcinolone acetonide injectable suspension in 2021, it's clear that the subretinal and suprachoroidal approaches have solid footing in the vitreoretinal armamentarium. It will be exciting to see how these delivery techniques evolve as they are used with novel therapies. ■

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**AARON NAGIEL, MD, PHD**
- The Vision Center, Children's Hospital Los Angeles
- Assistant Professor of Ophthalmology, Roski Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles
- anagiel@chla.usc.edu
- Financial disclosure: Consultant (Allergan Retina, Biogen/Nightstar, Regenxbio)

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Home monitoring may provide clinicians more reliable follow-up to help them provide proper treatment at the proper time. Moreover, it may reduce unnecessary office visits and ease the burden on patients. Still, larger prospective trials are required to determine patient uptake, compliance, and use rate, as well as reliability of home monitoring tools. ■

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**MATIAS IGLICKI, MD, PHD**
- Certified Teacher of Ophthalmology, University of Buenos Aires, Argentina
- matiasiglicki@gmail.com
- Financial disclosure: Consultant (Allergan, Bayer, Novartis, Genentech/Roche, TSK Laboratory); Investigator (Regeneron, Genentech/Roche)

**ANAT LOEWENSTEIN, MD, MHA**
- Director, Division of Ophthalmology, Tel Aviv Medical Center, Tel Aviv, Israel
- Vice Dean, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
- President, Israeli Ophthalmological Society
- anatl@tlvmc.gov.il
- Financial disclosure: Consultant (Allergan, Bayer, Beyeonics, Notal Vision, Novartis, Genentech/Roche)

**DINAH ZUR, MD**
- Head, Center for Retinal Degenerations; Senior Ophthalmologist, Ophthalmology Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
- dinagz@tlvmc.gov.il
- Financial disclosure: Consultant (Allergan, Bayer, Novartis, Genentech/Roche)

# Hypersonic Vitrectomy: A Different Perspective

Experts weigh in on the pros and cons of this new surgical tool.

BY SAMIR N. PATEL, MD; ASAEL PAPOUR, PHD; AND MICHAEL A. KLUFAS, MD

Hypersonic vitrectomy, unlike traditional vitrectomy systems, uses ultrasonic power to actuate the vitrectomy probe. Since the 2017 FDA approval of the Vitesse (Bausch + Lomb) hypersonic 100% open-port vitrectomy system, more than 50 surgeons in more than 10 countries have completed over 400 surgeries using the system. Although the technology is early in its deployment, it remains a promising tool for vitreoretinal surgery. In this article, we provide a background on this technology, ideal cases for which it can be used by any vitreoretinal specialist, and where the technology is headed.

## THE UPSIDE OF HYPERSONIC VITRECTOMY

Traditional vitrectors operate with guillotine-based cutters driven by a variety of different mechanisms. These systems aspirate vitreous fibers and cut them once they are inside the needle port. Recently, the ever-increasing cut rates of guillotine vitrectomy cutters have improved flow by decreasing the viscosity of aspirated vitreous; however, further improvements will be constrained by cut rate and duty cycle.

Hypersonic vitrectomy is a departure from this traditional technology. The Vitesse system operates as a single-lumen needle (currently 23-gauge) with an open-port design connected to a transducer that generates ultrasonic energy (Figure 1). That energy is transmitted through the needle to deliver focused tissue cutting capability by the port itself, with a mechanism of action described as mechanical shearing. As the port walls vibrate at ultrasonic frequencies, the incoming vitreous is sheared with a cut rate equivalent to millions of cuts per minute. This process changes the properties of the aspirated vitreous dramatically. The long collagen fibrils that are responsible for the mechanical properties of the vitreous are broken down to a microscopic size by the shearing action, such that it dramatically reduces the vitreous strength and apparent viscosity. This mechanism is designed to allow for continuous, uninterrupted, and efficient aspiration with a smooth action (Figure 2). It also reduces vitreous traction, as only sheared vitreous enters the inner needle lumen, in contrast to pneumatic cutters that first aspirate and then cut the vitreous.

Hypersonic vitrectomy is an attractive option from a clinical and practical perspective. It does not require high-pressure air infrastructure and may allow operation in almost any environment. In addition to practically eliminating noise and vibration, it can also cut and aspirate other substances and tissues, such as silicone oil and lens tissue.

Hypersonic vitrectomy technology and the single-needle lumen design removes some of the limitations of traditional pneumatic cutters including size, possibly allowing

## AT A GLANCE

- As the port walls of a hypersonic vitrectomy probe vibrate at ultrasonic frequencies, the incoming vitreous is sheared with a cut rate equivalent to millions of cuts per minute.
- Hypersonic vitrectomy can cut and aspirate vitreous and other tissue such as lens material.
- A prospective study reported outcomes of 50 real-world cases and noted technical issue in 46% of eyes that underwent hypersonic vitrectomy.


Image courtesy of Bausch + Lomb

Figure 1. The open port of the hypersonic vitrectomy needle delivers focused tissue cutting capability, shearing the vitreous with a cut rate equivalent to millions of cuts per minute.

for smaller needle gauge than 27 gauge and curved needle design. Furthermore, the single-needle design with a constantly open port should overcome the limitations created by the duty cycle and the double-needle designs of guillotine vitrectomy probes.

## THE DOWNSIDE

There are also potential disadvantages of the hypersonic vitrectomy system. A hypothetical concern related to the use of ultrasound-driven probes is the substantial heat production that may induce intraocular thermal damage.[1] This concern is particularly notable for intrascleral damage immediately proximal to the handpiece, given that there is an absence of intraoperative fluid that typically serves as a cooling agent. Retinal damage could be caused by a hypersonic vitrectomy probe but is mitigated by the cooling effect of cycling intraoperative fluid. Nonetheless, to address this concern, the hypersonic system uses polyamide- rather than metal-based cannulas.

Another theoretical concern may involve cavitation, which is the generation of vapor cavities in regions of very low pressure values with the potential to disrupt the surrounding retinal tissue. The occurrence of cavitations is a function of ultrasound power and needle design. Thus far, due to Vitesse's unique design and low power operation, the sytem has yet to produce any cavitation phenomena, even at the maximum stroke of 60 µm.[2]

Although the hypersonic vitrectomy system received FDA and CE clearance, there is only preliminary data in the literature regarding its safety and efficacy. Recently, a prospective multicenter study reported outcomes of 50 real-world cases and noted technical issue in 46% of eyes. The most common issue was inadequate vitreous liquefaction, leading to the formation of fibrous vitreous strands, in some cases accompanied by vitreous incarceration at the probe port. Because of these issues, 30% of procedures that started with hypersonic vitrectomy were converted to guillotine-based vitrectomy.[1] Another multicenter study of 64 patients reported inadequate vitreous liquefaction in 13% of cases.[3] From a surgical standpoint, the occurrence of inadequate vitreous liquefaction with the formation of vitreous strands can result in vitreoretinal tractions and, potentially, iatrogenic retinal tears.

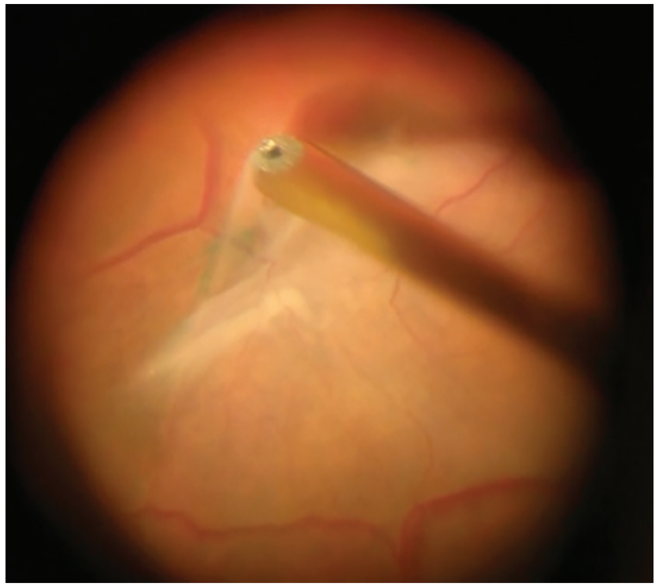
Image courtesy of Bausch + Lomb

Figure 2. Hypersonic vitrectomy may prove to be a useful tool for peeling membranes, as the mechanism of action allows for continuous and uninterrupted aspiration.

## HOW TO INTEGRATE HYPERSONIC VITRECTOMY INTO YOUR OR

To truly appreciate the fluidics of hypersonic vitrectomy, new users can consider trialing the system with a retained lens material surgery and silicone oil removal.

The hypersonic vitrectomy system can more efficiently remove silicone oil, particularly small emulsified droplets—a more difficult task with pneumatic guillotine cutters. The hypersonic probe fragments the silicone oil into tiny droplets, allowing for their aspiration out of the eye. During these cases, injecting triamcinolone into the vitreous cavity will allow the surgeon to better appreciate the fluidics of the system. In general, the sphere of influence of the hypersonic cutter is smaller and more precise that traditional cutters, acting more like a 27-gauge guillotine cutter rather than a 23-gauge guillotine cutter.

Retained lens material is another appropriate indication to evaluate the system for the first time and test the fluidics of the hypersonic vitrector, as the surgeon can usually forgo the need for a larger 20-gauge fragmatome.

Surgeons who use the Stellaris Elite system can switch between a 23-gauge guillotine cutter and the hypersonic handpiece throughout a procedure—no need to open an additional pack. This can be a nice feature to help surgeons integrate Vitesse into their surgical armamentarium.

It is helpful to have a knowledgeable company representative present for the initial cases, particularly when modulating the system features, such as stroke (ie, how far the probe moves, which influences how material enters the port), frequency, vacuum, and pulse mode. The features of a hypersonic system differ from traditional cutters when it comes to vacuum or changing to a biased closed duty cycle for shaving.

*(Continued on page 53)*

CODING ADVISOR

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# RETINA CODING: WHAT'S NEW IN 2022

Revised CPT codes will change how you code for common procedures, including retinal detachment prophylaxis and the new AMD therapy.

BY JOY WOODKE, COE, OCS, OCSR

## NEW CPT CODE DESCRIPTORS

**67141** Prophylaxis of retinal detachment (eg, retinal break, lattice degeneration) without drainage; cryotherapy, diathermy.

**67145** Prophylaxis of retinal detachment (eg, retinal break, lattice degeneration) without drainage; photocoagulation.

Each new year brings with it changes related to retina coding and reimbursement; this year, those changes are focused on retinal detachment prophylaxis codes and a new treatment for AMD. A comprehensive understanding of these changes will avoid costly denials and inappropriate reimbursement.

## RETINAL DETACHMENT PROPHYLAXIS

The most significant change affecting retina practices is the descriptor and value for CPT codes **67141** and **67145**. These two codes were revised, and the language "one or more sessions" was removed from the descriptor. Additionally, the codes were revalued, and the global period was revised from 90 days to 10 days (Table).

### Impact On Coding

With the change in the global period, these two codes are now considered minor procedures, a significant change when

THE MOST SIGNIFICANT CHANGE AFFECTING RETINA PRACTICES IS THE DESCRIPTOR AND VALUE FOR CPT CODES 67141 AND 67145.

examinations are performed on the same day. The -57 modifier, decision for major surgery, would no longer be used and the -25 modifier should be considered. A significant, separately identifiable examination would need to be performed and documented to append the -25 modifier. Although medically necessary, if the examination was performed to confirm the need for the prophylaxis of retinal detachment by cryotherapy or laser, it would not be billable separately.

### Payer Nuances

Although CMS has revised the global period from 90 days to 10 days, some payers may delay implementation. For example, when CPT code 67228 was assigned a 10-day global period in 2016, many payers continued with a 90-day global period. In fact, some Medicaid payers continue to recognize

**TABLE. REVALUED CODES WITH REVISED 10-DAY GLOBAL PERIOD**

| CPT Code | Global Period | 2021 Facility Allowable | 2022 Facility Allowable | 2021 Non-Facility Allowable | 2022 Non-Facility Allowable |
|---|---|---|---|---|---|
| 67141 | 10-days | $488.85 | **$210.66** | $531.42 | **$264.75** |
| 67145 | 10-days | $499.32 | **$210.66** | $533.86 | **$237.20** |

CPT code 67228 as major surgery with a 90-day global period. If the payer assigns a 90-day global period, the same-day examination would be billed with the -57 modifier.

## NEW TREATMENT FOR AMD

Last year, the FDA approved the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) for patients with wet AMD who previously responded to at least two intravitreal injections of anti-VEGF. This device provides continuous delivery of the anti-VEFG agent via an implant. After the initial fill and implant, a refill-exchange procedure is provided at approximately 6 months.

The initial procedure, including the fill and implant, is done in an ambulatory surgical center or hospital outpatient department. The facility submits CPT code 67027 for the procedure, along with a generic HCPCS code J3490, J3590, or C9399 for the medication. For the CMS 1500, report the NDC in item 24a in 5-4-2 format, 50242-0078-55, and the medication name, dosage, and invoice amount in item 19. If performed in a hospital outpatient department, the facility should also submit C1889 for the implant.

The physician claim for the initial fill and implant should submit CPT code 67027 and the appropriate anatomical modifier (eg, -RT or -LT).

For the refill-exchange procedure, typically provided in-office, the physician should report CPT code 67028 and the anatomical modifier. The medication is reported with generic HCPCS code J3490 or J3590. Submit the NDC in item 24a in 5-4-2 format, 50242-0078-12, and the medication name, dosage, and invoice amount in item 19.

## NEW YEAR, NEW COMMITMENTS

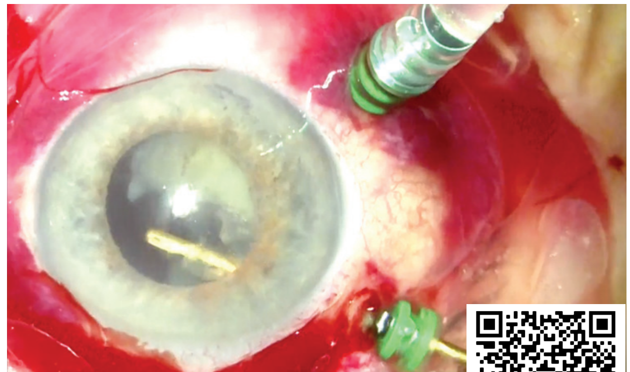
Throughout 2022, a commitment to mastering coding changes and their impact on payer policy will be key—particularly as we look forward to more FDA approvals. The AAO will be providing education at aao.org/retinapm and at a Codequest near you. The schedule can be found at aao.org/codequest. ■

**JOY WOODKE, COE, OCS, OCSR**
- Coding and Practice Management Executive, American Academy of Ophthalmology, San Francisco
- jwoodke@aao.org
- Financial disclosure: None



*(Continued from page 50)*

**WATCH IT NOW**



Hypersonic Vitrectomy For Removing Retained Lens Material

## FUTURE DIRECTIONS

Surgeon feedback led to the development of an optimal device configuration for the latest iteration of the hypersonic vitrectomy system, including a higher frequency setup, new control software, and a new port design. A 25-gauge system is also under development. Future technical advances may further increase the range of ultrasound power.

Hypersonic vitrectomy offers retina specialists a rare opportunity to help change the landscape of surgery with a disruptive technology. For eager surgeons with an open mind, hypersonic vitrectomy holds far more potential than just ‘ultrasound with a 1 million cut rate.’ The technology, still under investigation and development, aims to potentially become a mainstream vitreoretinal surgical option. ■

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**MICHAEL A. KLUFAS**
- Vitreoretinal Surgeon, Assistant Professor of Ophthalmology, Wills Eye Hospital, Mid Atlantic Retina, Sidney Kimmel Medical College and Thomas Jefferson University, Philadelphia
- mklufas@gmail.com
- Financial disclosure: Consultant (Allergan, Genentech/Roche); Speaker (Genentech/Roche, Regeneron)

**ASAEL PAPOUR, PHD**
- Senior Principal Scientist, Bausch + Lomb
- Financial disclosure: Employee (Bausch + Lomb)

**SAMIR N. PATEL, MD**
- Vitreoretinal Surgery Fellow, Wills Eye Hospital, Mid Atlantic Retina, Sidney Kimmel Medical College and Thomas Jefferson University, Philadelphia
- sapatel@midatlanticretina.com
- Financial disclosure: None Acknowledged

# AN UNUSUAL CASE OF UNILATERAL PURTSCHERS RETINOPATHY


We saw a rare presentation of vision loss in preeclampsia—but only in one eye.

BY AARON S. CAMPEAS, BSC, AND BOLESLAV KOTLYAR, MD

In 1910, Otmar Purtscher published an article describing a patient with bilateral vision loss after head trauma.[1] On examination, the patient had retinal hemorrhages and whitening in the posterior pole in each eye. This chorioretinopathy associated with trauma or systemic injury—which has findings of cotton-wool spots, retinal hemorrhage, optic edema, and areas of retinal ischemia—is now called Purtschers retinopathy. Etiologies of this condition include pancreatitis, fat embolism, air embolism, amniotic fluid embolism, HELLP syndrome, trauma, long bone fracture, preeclampsia, and eclampsia.[2] Despite the many potential causes, Purtschers retinopathy is extremely rare, with one study finding an incidence of only 0.24 cases per million per year in the United Kingdom and Ireland.[3]

We report the case of a woman with preeclampsia who experienced acute unilateral vision loss secondary to Purtschers retinopathy. Our literature review using PubMed and Scopus to search “preeclampsia Purtscher retinopathy” found no other cases of unilateral visual involvement of Purtschers retinopathy in patients with preeclampsia.

## CASE REPORT

A 23-year-old Black woman who was 27 weeks pregnant presented to the ophthalmologist with decreased vision in her right eye for 3 days. Past medical history was significant for anemia, managed with iron and prenatal supplements. On examination, BVCA was 20/250 OD and 20/20 OS. No afferent pupillary defects were present. Anterior segment examination and IOP were unremarkable in each eye. On fundoscopy, the left eye was unremarkable. Fundoscopy of the right eye revealed dilated veins with scattered inferior peripapillary flame-shaped hemorrhages, cotton-wool spots, and Purtscher flecken (Figure 1). OCT showed retinal thickening, subretinal fluid, and nerve fiber layer edema (Figure 2). Fluorescein angiography was deferred due to pregnancy, and her blood pressure was 174/122. Given these findings, a diagnosis of Purtschers retinopathy was made, likely due to preeclampsia.

Due to the presumptive diagnosis of preeclampsia, the patient was urgently referred to her obstetrician. The patient did not follow up with the obstetrician as recommended but presented to the emergency department 1 week later. She had a blood pressure of 168/94 and 4+ proteinuria. She was diagnosed with preeclampsia, a Cesarean section was performed 2 days later, and two healthy babies were delivered.

Eleven weeks postpartum, the patient’s VA was counting fingers OD. Fundus examination showed inferior optic nerve pallor. There was normalization of the retinal vascular caliber. The subretinal fluid and macular edema had almost resolved. Fluorescein angiography showed normal transit time with hypofluorescence in a wedge-shaped area inferotemporally and peripheral nonperfusion (Figure 3). Fine lacy collateral vessels were seen adjacent to areas of nonperfusion. No late leakage was present centrally. The patient’s findings were consistent with postinflammatory optic atrophy and sequelae of retinal ischemia due to Purtschers retinopathy. As of publication, visual acuity remained counting fingers OD.

## DISCUSSION

Preeclampsia is a systemic vascular disorder characterized by hypertension, end organ damage, endothelial dysfunction, and hypercoagulability. Preeclampsia occurs in 3% to 5% of pregnancies, and visual changes can be seen in 25% of severe cases. Common visual complaints include blurred vision, photopsia, visual field defects, and blindness. Vision loss can be caused by serous retinal detachment, focal necrosis of retinal epithelial cells, cortical blindness, central retinal vein occlusions, and Purtschers retinopathy.[4]

Purtschers retinopathy is an arteriolar microvascular disease characterized by occlusion of the 45 µm-diameter peripapillary arterioles that supply the superficial retinal capillaries. Patients typically present with acute vision loss. Common fundoscopic findings are cotton-wool spots (93% of cases), retinal hemorrhages (65%), and Purtscher flecken (63%). The diagnosis of Purtschers retinopathy should be suspected in cases with any of these three signs.[5]

One study recorded data at the 1- and 6-month marks for patients (24 total eyes) with Purtschers retinopathy. At

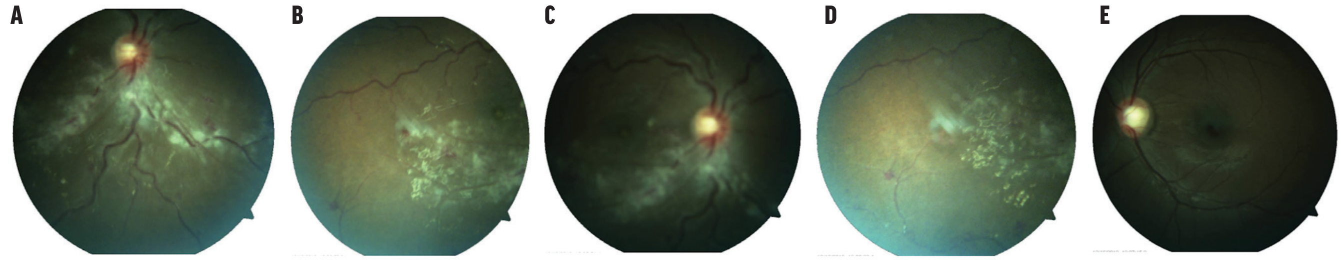


Figure 1. Fundoscopic imaging of the right eye revealed dilated veins (A), cotton-wool spots (B), hemorrhages (C), and Purtscher flecken (D). The left eye was unaffected (E).

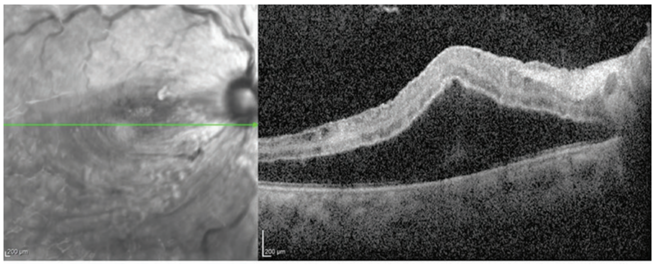

Figure 2. OCT showed retinal thickening consistent with macular edema, subretinal fluid, and nerve fiber layer edema.

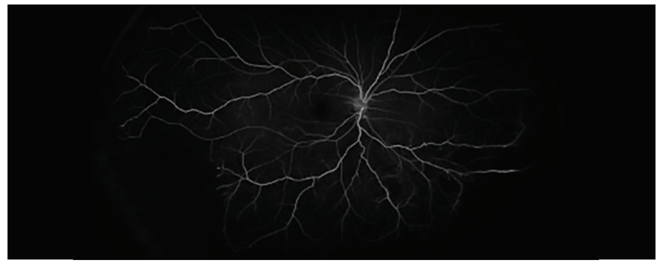

Figure 3. Fluorescein angiography displays hypofluorescence in a wedge-shaped area

1 month, 74% of eyes still had acute retinopathy findings of hemorrhages, cotton-wool spots, or Purtscher flecken. At 6 months, 100% of acute retinal findings had disappeared. In addition, 50% of eyes had VA improvements by 2 lines and 23% by 4 lines, with a mean improvement of 2.7 lines. Final VA remained 20/200 or less in 11 of 24 eyes.[3] Another review found that 10 of 25 patients had a final VA of 20/200 or less in at least one eye at their final vision assessment.[6]

Treatment for Purtschers retinopathy is typically limited to the treatment of the underlying condition (in our case, the condition of preeclamptic pregnancy) and waiting for symptom resolution. Isolated case reports have shown visual improvements after administering a 3-day course of 250 mg intravenous methylprednisolone four times a day. A proposed mechanism of improved outcomes with high-dose corticosteroids is the stabilization of damaged neuronal membranes to allow for healing.[2] One case report detailed a patient with Purtschers retinopathy who improved from 20/800 to 20/50 at 1 week post methylprednisolone.[7]

Another report detailed two eyes with Purtschers retinopathy treated with methylprednisolone. Only one improved by 2 or more lines, and neither eye showed improvement greater than 4 lines.[3] Given the small quantity of data and varying results, corticosteroids are not recommended.

The unilateral involvement of our patient is perhaps a result of anatomic arteriolar vascular differences between the right and left eyes. Flow studies suggest Purtschers retinopathy may be the result of the interplay between the angle of bifurcation, flow volume, capillary wall stress and levels of endothelin peptide, prostacyclin, nitric oxide, and local autoregulation.[8] In our case, the increased flow rate due to preeclampsia-induced hypertension may have led to changes in wall stress. Differences in the angles of bifurcation in the microvasculature between the left and right eyes may have led to different degrees of wall stress, thus resulting in unilateral involvement.

## CONCLUSION

Delayed diagnosis and intervention with preeclampsia can result in permanent damage to end organs, including the eyes. Our case emphasizes the need to aggressively treat these patients, often by expedited delivery. In the absence of effective treatments for acute occlusive retinal vascular disease, prevention through vigilance and managing systemic risk factors are our best available approaches to preventing vision loss. ■

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**AARON S. CAMPEAS, BSC**
- Student, Touro College of Osteopathic Medicine, New York, New York
- acampeas@student.touro.edu
- Financial disclosure: None

**BOLESLAV KOTLYAR, MD**
- Retinal Surgeon, Vitreous Retina Macula Specialist of New Jersey, Millburn, New Jersey
- Retinal Surgeon, Eyecare Partners, Millburn, New Jersey
- boleslav.kotlyar@gmail.com
- Financial disclosure: None

# A PRIMER ON IN-OFFICE RETINAL PROCEDURES


Take the proper steps now to minimize problems down the road.

BY ADAM PFLUGRATH, MD, AND STEVE CHARLES, MD, FACS, FICS

Performing in-office procedures comes with the territory of being a vitreoretinal surgeon. You can often use these techniques to resolve common problems, even selected postoperative complications, without a trip to the OR. By minimizing repeat operations, you can save time and costs, and give patients a positive experience.

This article reviews the most effective approaches to several in-office retinal procedures.

## IN-OFFICE BASICS

Almost all in-office retina procedures start with the same basic steps.

- You, the patient, and your technician should all wear surgical masks due to the proximity of oral and nasal bacteria. You can also tape the patient's mask over the nose to further minimize transmission of oral and nasal bacteria to the procedure site.
- Lay instruments on a sterile drape.
- Wear sterile gloves while manipulating the sterile eyelid speculum and in case of inadvertent contact with any needles.
- Clean the eyelids and lashes with povidone iodine. You can instill topical 2% lidocaine, proparacaine, or tetracaine prior to 5% povidone iodine (betadine) to further minimize discomfort. Povidone iodine is currently the proven antiseptic. Because iodine is required for essential functions of the thyroid gland, an allergy to iodine cannot exist.[1] You can reduce irritation of the skin and corneal epithelium with post-procedure irrigation with sterile saline or balanced salt solution. Additionally, use of preservative-free artificial tear lubricants may greatly reduce irritation and discomfort after the procedure, as well as a drop of a topical NSAID before.[2]
- Depending on the procedure in question, subconjunctival lidocaine may be required.
- Use a sterile, bladed eyelid speculum to expose the procedure site and contain the eyelashes. Use a separate sterile eyelid speculum for each eye.

## INTRAVITREAL INJECTIONS

Do not perform an intravitreal injection in the presence of blepharitis or conjunctivitis, unless for the treatment of endophthalmitis. Complete an appropriate slit lamp examination of the eyelids and conjunctiva before performing intravitreal injections to ensure these conditions are not present. In addition, do not stop anticoagulants prior to intravitreal injection or other procedures; doing so places patients at increased thromboembolic risk, for which the anti-VEGF medication may be incorrectly blamed.[3]

Patients are first prepped using the steps outlined above. Subconjunctival lidocaine is usually not required, as the risk of perforation, pain of anesthetic injection, and patient discomfort outweigh the value of additional anesthesia. The injection site should be 3.5 mm to 4 mm posterior to the limbus, depending on lens status. Instill a drop of povidone iodine over the injection site after placing the eyelid speculum and immediately before injection. Give the patient a fixation point. We typically perform injections in the inferotemporal quadrant due to the natural Bells reflex many patients experience; it also helps to avoid the superior quadrants in patients who have had prior glaucoma filtering surgery. Assess retinal circulation with indirect ophthalmoscopy and confirm counting fingers VA after each injection.

## PARS PLANA TAP WITH AND WITHOUT ANTIBIOTIC INJECTION

A pars plana tap is necessary in the case of IOP elevation with excessive oil or gas, with gas mixture–related overexpansion, and for removal of a sufficient sample for microbiologic laboratory analysis in the setting of endophthalmitis. After the initial preparation, we typically use subconjunctival 2% lidocaine, in addition to topical anesthetic drops, to obtain adequate anesthesia.

For gas overfills or gas mixture–related overexpansion, a 30-gauge needle on an empty tuberculin syringe with the plunger removed (thus open to the atmosphere) inserted through the pars plana will allow passive egress of gas to equilibrate the IOP. For removal of silicone oil, a 25-gauge needle on a tuberculin syringe open to the atmosphere or a 25-gauge non-valved trocar, inserted at a 15° angle to create a self-sealing wound, is required. The elevated IOP is sufficient to allow for egress of excess silicone oil through a non-valved trocar or empty tuberculin syringe.

In cases of endophthalmitis, insertion of a 27-gauge valved trocar through the pars plana 3.5 mm to 4 mm from the limbus, at a 15° angle, is ideal. The trocar method allows for the collection of vitreous sample and injection of antibiotics through a single injection site, as opposed to multiple injections, reducing patient discomfort. In the setting of inadequate vitreous sample volume removal with intravitreal injection of antibiotics, an anterior chamber paracentesis (outlined below) is required to sufficiently lower IOP.

## PNEUMATIC RETINOPEXY

This is a highly effective method of primary repair for superior retinal detachments (RDs) with single or multiple closely grouped breaks. Although pneumatic retinopexy has been a useful technique since the late 1980s, it has been used less frequently in recent years due to the advent of and greater reattachment success rates with transconjunctival, sutureless 25- and 27-gauge pars plana vitrectomy (PPV).[4]

We typically use topical tetracaine, proparacaine, or 2% lidocaine, along with subconjunctival 2% lidocaine anesthesia. Rarely, retrobulbar or peribulbar anesthesia is required. Prep the patient using the steps above, and position the patient on his or her side, rather than in a supine or seated position.

We use $C_3F_8$ gas, rather than $SF_6$ gas or air, due to the three-to-four times greater expansion of $C_3F_8$ compared with air ($SF_6$ expands two times greater than air). We inject 0.6 cc of 100% $C_3F_8$ gas using a 1-cc tuberculin syringe on a 30-gauge needle, although the optimal volume is controversial.[5] Slower gas injection, along with injection at the highest point with the needle inserted just through the pars plana, is key to avoiding multiple small bubbles, or "fish eggs." The use of 0.6 cc $C_3F_8$ gas requires an anterior chamber paracentesis after the procedure, given the increase in IOP. Use of a small-diameter needle and changing the patient's position immediately following the injection will minimize the risk of gas leaking through the injection site.

Retinal breaks are typically treated 1 to 2 days, followed with laser indirect ophthalmoscope (LIO) retinopexy after reattachment. If there is an insufficient view, limiting the use of LIO, you can perform pre- or post-reattachment transscleral cryotherapy.

## ANTERIOR CHAMBER PARACENTESIS

In our clinical practice, anterior chamber paracentesis is used after pneumatic retinopexy or anti-VEGF injection and to relieve IOP for the urgent treatment of viscosity or particulate glaucoma.[6]

**Figure. Two-needle fluid-gas exchange needle and syringe equipment.**

Perform anterior chamber paracentesis at the slit lamp with an eyelid speculum in place and the patient seated upright. Instill 5% povidone iodine, unless it was recently used for intravitreal injection or pneumatic retinopexy. Place a 30-gauge needle through the inferior limbus parallel to the iris plane at an oblique angle into the anterior chamber. Needle placement over the iris, as opposed to directed toward the pupil, decreases the risk of inadvertent lens touch or damage. Entering at an oblique angle also ensures a self-sealing wound. You can repeat anterior chamber paracentesis as needed to adequately lower IOP once the chamber sufficiently refills.

Do not use anterior chamber paracentesis in cases of elevated IOP secondary to anterior chamber silicone oil emulsification while silicone oil remains in the vitreous cavity or to relieve IOP secondary to gas mixture–related overexpansion. These complications require a repeat PPV with silicone oil removal and a pars plana tap, respectively.[6]

## TWO-NEEDLE ANTERIOR CHAMBER WASHOUT

In cases of particulate glaucoma due to retained perfluoro-carbon-liquid (PFCL) or emulsified silicone oil in the anterior chamber, perform a two-needle anterior chamber washout to remove the causative agent.[6] For this technique, use one needle to infuse balanced salt solution and a second needle for droplet egress—maintaining the anterior chamber throughout the procedure.

Prep the patient as outlined above. Fill a 10-cc syringe with balanced salt solution and attach it to sterile 7-inch extension tubing and a 30-gauge needle. Attach the second 30-gauge needle to a tuberculin syringe open to the atmosphere to allow for droplet egress.

For retained PFCL, position the patient seated at the slit lamp. Place the infusion needle superiorly at an oblique angle into the anterior chamber through the limbus parallel to the iris plane. Insert the egress needle in a similar manner, while staying over the iris with the bevel facing upward at the 6:00 clock position to facilitate PFCL egress. The assistant then slowly pushes the balanced salt solution syringe to allow egress of fluid through the empty tuberculin syringe. Once sufficient PFCL droplets have been removed, turn the egress needle to the bevel down position to remove any additional PFCL droplets in the angle. Remove the egress needle, and adjust IOP with the balanced salt solution syringe.

In the case of silicone oil emulsification in the anterior chamber, the procedure is similar to that for PFCL droplet removal. Unlike PFCL, however, silicone oil emulsification floats in aqueous, and the patient must be supine while you use an operating microscope or loupes. Place the infusion and egress needles at comfortable locations for you to insert the needles at an oblique angle, again parallel to the iris plane and staying over the iris. Insert the egress needle with the bevel facing upward and rotate it along the limbal axis to the proper location to avoid lens damage. The assistant then slowly pushes the balanced salt solution syringe to allow egress of fluid. Be careful to avoid damaging the corneal endothelium during silicone oil removal.

## TWO-NEEDLE FLUID-GAS EXCHANGE

Occasionally, patients may develop recurrent RDs or vitreous hemorrhage following PPV. Additionally, some macular holes fail to close following repair. In these scenarios, assuming prior adequate vitreous removal, perform an in-office two-needle fluid-gas exchange through the pars plana using an iso-expansile concentration of $SF_6$ gas (25%).

The preparation is similar to that of a pneumatic retinopexy, with the patient positioned on his or her side with the eye in question down (ie, for right eyes, patients should be on their right side). In this position, the nasal side of the eye is the highest point, at which you can insert a 30-gauge needle 3.5 mm to 4 mm posterior and perpendicular to the limbus. Advance the needle 2 mm to 3 mm through the pars plana to minimize the formation of "fish eggs." Attach this superior injection needle to 7-inch extension tubing and a 60-cc iso-expansive air-gas filled syringe operated by an assistant (Figure).

Place a second 27- or 30-gauge egress needle at the lower most part of the eye, temporally, again 3.5 mm to 4 mm from the limbus. Attach the needle to a tuberculin syringe with the plunger removed to act as a handle. Direct the open end of the tuberculin syringe over a waste can to collect the fluid. The assistant slowly pushes the iso-expansile gas mixture syringe, and egress of fluid may be noted through the lower syringe. Continue the exchange until the air-gas mixture is observed through the egress needle. Slowly withdraw the egress needle while tilting it slightly to ensure a full gas fill. Adjust IOP using the air-gas infusion syringe, along with tactile assessment of the IOP with a gloved fingertip.

Once IOP has been appropriately adjusted, remove the nasal air-gas infusion needle, and position the patient based on lens status and tear/hole location. In the case of post-PPV RD, you can often perform LIO laser retinopexy the same day as the two-needle fluid-gas procedure, if reattachment has occurred.

## CONCLUSION

Using the above in-office procedures, many problems encountered in the retina practice can be effectively and efficiently resolved, minimizing costly and frustrating repeat trips to the OR. ■

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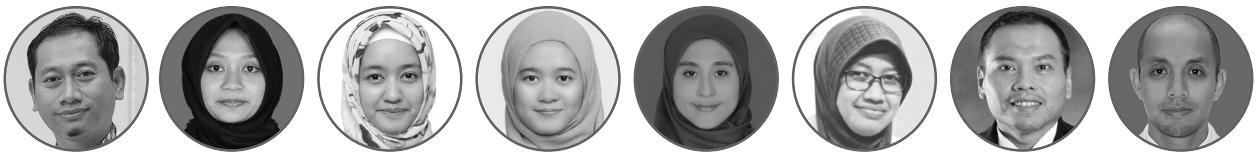
**STEVE CHARLES, MD, FACS, FICS**
- Retina Surgeon and Founder, Charles Retina Institute, Germantown, Tennessee
- Editorial Advisory Board Member, *Retina Today*
- scharles@att.net
- Financial disclosure: None

**ADAM PFLUGRATH, MD**
- Retina Surgeon, Jervey Eye Group, Greenville, South Carolina
- AEP@jervey.com
- Financial disclosure: None

# COMBINED PUPILLOPLASTY AND IRIS-FIXATED IOL IMPLANTATION



A novel technique for treating complicated aphakia with atonia and insufficient capsular support in vitrectomized eye.

BY SUPANJI SUPANJI, MD, MSC, PHD; DINDA AJENG ANINDITA, MD; IZZATI AMAYAZIFUN KHALIFA FARZANA, MD; ANINDITA DIANRATRI, MD; WIDYA ARDHANA RESWARI, MD; NURUL IMAWATI, MD; IMAM TIHARYO, MD, MSC; AND MUHAMMAD BAYU SASONGKO, MD, MEPID, PHD

Repairing surgically aphakic patients who have had a previous vitrectomy is complicated due to insufficient capsular support and/or major alterations in the anatomy of the anterior chamber, especially in the presence of iris defects.[1,2]

A significant cause of iris defects is pupil atonia, one of the most common complications of anterior segment surgery. In one survey, 60% of responding cataract and refractive surgeons encountered at least one case of pupil atonia after cataract surgery in the last 5 years.[3,4] Light sensitivity is common in patients with an atonic pupil secondary to trauma; thus, these cases require a challenging surgical technique for repairing the defects.[5,6]

Pupilloplasty, commonly used to repair damage associated with iris dysfunction, recreates the proper size of the pupil while maintaining the structural integrity of the iris tissue. Trauma, postoperative sequelae, elevated IOP, chronic uveitis, herpes simplex virus, herpes zoster virus, and proliferative disorders can all have a substantial impact on physiological pupillary dimensions, and as such, the iris must be thoroughly assessed for proper management of the defect.[1,7]

## CASES

The primary consideration of our study was whether iris dysfunction may be repaired with a combination of pupilloplasty and iris-fixated IOL implantation. In most trauma cases, the defect can only be repaired using the suturing technique. However, in the case of proliferative diseases such as iridocorneal endothelial syndrome or epithelial down growth, prosthesis is required to replace an iris in poor condition.[1,8]

Cases of iris defect in aphakic-vitrectomized eyes present ophthalmologists with a whole new set of challenges, considering even typical treatments are complex and difficult. Using a case series approach, we describe the management of three aphakic vitrectomized patients (three eyes) who have a pathologically wide pupil (atonia) and insufficient capsular support. We used the single-pass four-throw (SFT) approach with a secondary iris-fixated IOL implantation.

Vitrectomy and lensectomy were performed in patients with nucleus drop or posterior luxation of cataract. After 1 month, pupilloplasty and IOL implantation using an artisan iris-fixated technique were performed. All surgical procedures were performed by the same surgeon (S.S.).

We chose the SFT technique because it provides some advantages over other techniques, including reduced surgical manipulation, fast surgical time, and dissemination of the pigment in previously compromised eyes.[7,8] It also offers faster rehabilitation and reduced inflammation in postoperative settings.[9] Recently, interest in the SFT technique has grown because it can significantly reduce photophobia and glare.[10,11] All procedures were performed under local anesthesia (topical pantocaine and intracameral lidocaine 2%) under monitored care.

## SURGICAL STEPS

The first step in the pupilloplasty is to make a small incision in the cornea and fill the anterior chamber with lidocaine, carbachol, and viscoelastic materials. Then, make two incisions on either side in the limbus along the axis of the iris defect. Using a 26-gauge needle, introduce a polypropylene

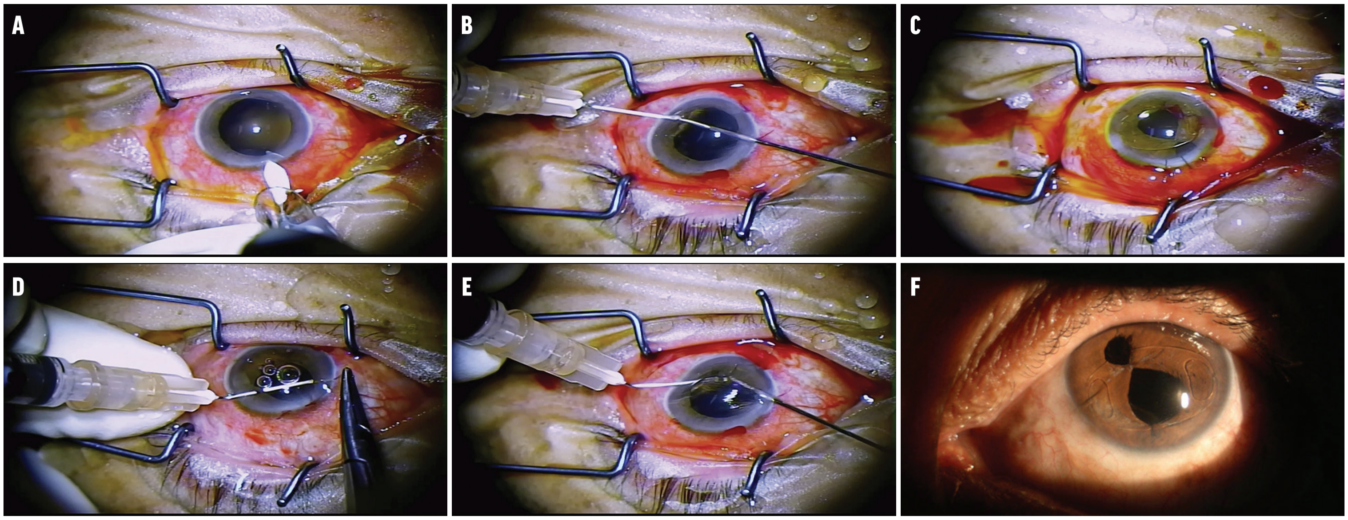


Figure 1. During pupilloplasty using the SFT technique in case number one of an aphakic-vitrectomized eye, a small incision is introduced to fill the anterior chamber with lidocaine, carbachol, and viscoelastic materials (A). Then, two incisions are made on both sides of limbus, along the axis of iris defect (B). A 26-guage needle is introduced into the anterior chamber and passed through the iris tissue (C). The 26-guage needle is pulled along with the suture, then securely tied (D). In the contralateral side (the upright side of the iris), procedures B and C are repeated until proper pupil size is achieved (E). The artisan IOL is inserted, and the lens is properly enclavated in the anterior chamber (F).

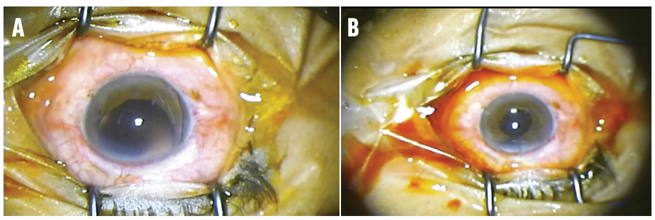


Figure 2. Before pupilloplasty in case number two, the patient has a pathologic large pupil in an aphakic-vitrectomized eye (A). Postoperatively, a well-rounded pupil was achieved and the IOL was well implanted (B).

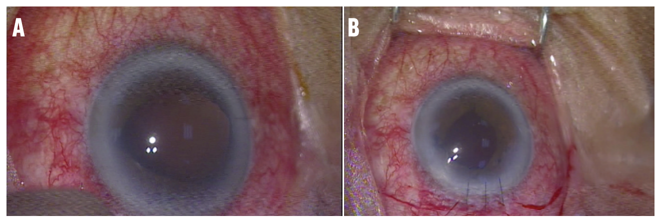


Figure 3. Preoperatively, the third patient in the series has a pathologically large pupil in an aphakic-vitrectomized eye (A). The condition of the pupil and retropupillary iris-fixated IOL improved after the reconstruction was complete (B).

suture through the limbal incision, passing straight through the iris (1 mm from pupil) and exiting through the contralateral side of the iris. Tie the suture securely and repeat the procedure until the normal pupil size is achieved.

After the pupilloplasty procedure is complete, insert an iris-fixated IOL into the anterior chamber while avoiding the previous suture. Adjust the optical part of the IOL with the pupil's position, then enclave the IOL. Perform an iridectomy, remove the viscoelastic, and suture the cornea.

All three cases used SFT pupilloplasty without iris prosthesis (Figures 1-3). Follow-up examinations were scheduled up to 3 months postoperative to assess the success of the procedure by comparing visual acuity and IOP at baseline and 3 months after the operations.

## RESULTS

In all three patients, visual acuity showed significant improvement 3 months postoperative (Table). This result was similar to a previous study in which uncorrected visual acuity rose significantly from 1.15 ± 0.29 logMAR to 0.37 ± 0.17 logMAR at 6 months after surgery ($P < .05$).[3]

In addition, IOP from admission date to 3 months after surgery showed normal results with a range of 16 mm Hg to 17 mm Hg for all patients. The mean preoperative IOP was

**TABLE. DEMOGRAPHICS AND OUTCOMES**

| Case | Gender | Affected Eye | Age (years) | Uncorrected Visual Acuity (Snellen Chart) | | IOP (mm Hg) | |
|---|---|---|---|---|---|---|---|
| | | | | Preoperative | 3 months postoperative | Preoperative | 3 months postoperative |
| 1 | Male | Left | 62 | 1/60 | 6/60 | 17 | 17 |
| 2 | Female | Right | 57 | 0.5/60 | 6/12 | 18 | 16 |
| 3 | Male | Right | 58 | 1/60 | 6/40 | 18 | 16 |

17.7 ± 0.58 mm Hg; 3 months after surgery, mean IOP was 16.4 ± 0.58 mm Hg. A similar result was reported in another study, in which iris-fixated IOL implantation with pupilloplasty did not affect IOP up to 6 months after surgery.[3]

## DISCUSSION

Iris reconstruction is necessary with atonia, as the quality of vision is significantly affected by permanent mydriasis of the pupil; patients may experience a wide range of visual disturbances such as glare, starburst, ghosting phenomena, and photophobia.[12]

Because of cosmetic concerns, surgeons should repair the iris to achieve improved functional and aesthetic outcomes.[12] All three patients included in this study were satisfied with the surgery, given that their visual acuity improved significantly and their symptoms of glare and photophobia reduced remarkably.

According to a meta-analysis conducted by Jing et al, the iris-fixated IOL procedure requires a surprisingly short surgical time due to the use of a corneal incision and IOL push-in.[13] This simpler process could lead to a noninvasive manipulation of the eye, reducing the potential for complications. Based on one author's experiences (S.S.), since the vitrectomized globe is at a higher risk of collapsing during the procedure, surgeons must monitor IOP carefully. If IOP drops, the globe must be filled with balanced salt solution immediately.

In our study, there were no complications reported by any patient during surgery or in 3 months of routine monitoring. Nonetheless, complications have been reported in previous studies, including temporary increase in IOP, hemorrhage, choroid effusion, and pigment adhesion.[3]

## CONCLUSION

Our results support previous findings that the combination of pupilloplasty and iris-fixated IOL implantation under local anesthesia can be a quick and simple way to treat aphakic-vitrectomized eyes with insufficient capsular support and atonia. Further studies with a larger sample size may provide additional insights on the use of this approach. ■

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**SUPANJI SUPANJI, MD, MSC, PHD**
- Vitreoretinal Surgeon, Dr. Sardjito General Hospital; Ophthalmology Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta; Dr. S. Hardjolukito Air Force Hospital, Yogyakarta Indonesia
- supanji@ugm.ac.id
- Financial disclosure: None

**DINDA AJENG ANINDITA, MD**
- Medical Doctor, Dr. Sardjito General Hospital; Ophthalmology Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
- Financial disclosure: None

**IZZATI AMAYAZIFUN KHALIFA FARZANA, MD**
- Medical Doctor, Dr. Sardjito General Hospital; Ophthalmology Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
- Financial disclosure: None

**ANINDITA DIANRATRI, MD**
- Medical Doctor, International SOS, Jakarta, Indonesia
- Financial disclosure: None

**WIDYA ARDHANA RESWARI, MD**
- Ophthalmologist, Dr. Sardjito General Hospital; Ophthalmology Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
- Financial disclosure: None

**NURUL IMAWATI, MD**
- Ophthalmologist, Dr. S. Hardjolukito Air Force Hospital, Yogyakarta, Indonesia
- Financial disclosure: None

**IMAM TIHARYO, MD, MSC**
- Ophthalmologist, Cataract and Refractive Surgery Consultant, Sultan Agung Islamic Hospital, Semarang, Indonesia
- Financial disclosure: None

**MUHAMMAD BAYU SASONGKO, MD, MEPID, PHD**
- Vitreoretinal Surgeon, Dr. Sardjito General Hospital; Ophthalmology Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
- Financial disclosure: None

# CME SECONDARY TO EXTRA-MACULAR CHOROIDAL MELANOMA

A rare case of ocular melanoma with retinal invasion leading to remote cystoid macular edema.

BY ANKUR NAHAR, BS; AHMED SHEIKH, MD; AND CAROL L. SHIELDS, MD

Uveal melanoma expresses VEGF, which promotes tumor angiogenesis and growth.[1-3] A study by Missotten et al found that eyes with uveal melanoma displayed median VEGF concentrations of 146 pg/mL compared with 50.1 pg/mL in controls.[2] Eyes with retinal detachment had median VEGF levels of 43.5 pg/mL, suggesting the high VEGF levels in uveal melanoma cannot be explained by the presence of retinal detachment alone.[2] The study also demonstrated eyes that underwent radiation therapy for uveal melanoma had even higher median VEGF concentrations at 364 pg/mL.[2] Specifically, after proton beam radiotherapy, VEGF levels were 1,058 pg/mL and 3,000 pg/mL in two eyes; after plaque radiotherapy, VEGF levels ranged from 79 pg/mL to 555 pg/mL in four eyes.[2]

Despite elevated levels of intraocular VEGF in uveal melanoma, cystoid macular edema (CME) is rarely found prior to treatment.[1,4] We describe a patient who presented with unilateral CME and was later detected to have a post-equatorial extra-macular choroidal melanoma.

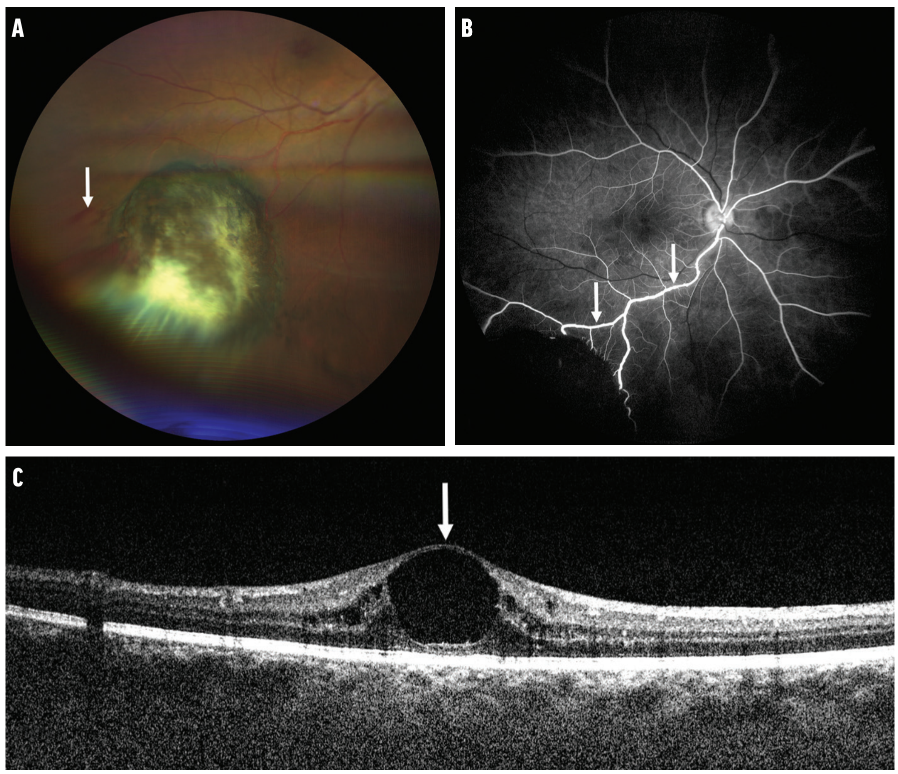


Figure 1. Wide-angle fundus photography revealed a choroidal melanoma with overlying acute vitreous hemorrhage (arrow, A). There is also white vitreous fibrosis from chronic hemorrhage. Intravenous fluorescein angiography showed a slightly dilated and beaded feeding retinal arteriole (arrows, B). Note the melanoma is hypofluorescent due to retinal invasion. OCT revealed prominent CME with 640 µm in average central thickness (arrow, C).

## CASE REPORT

A healthy 42-year-old Hispanic man noted blurred vision in his right eye and was found to have “fluid” in the retina, initially diagnosed at another clinic as central serous chorioretinopathy (CSCR). At 10 months follow up, there was persistent fluid, and further inspection revealed a newly detected choroidal mass. He was referred to our Ocular Oncology Service for evaluation.

The patient denied diabetes mellitus and was otherwise healthy. On presentation, VA was 20/200 OD and 20/40 OS. The anterior segment was unremarkable in each eye. Dilated fundus examination demonstrated no abnormalities in the left eye. In the right eye, a pigmented choroidal melanoma was noted inferotemporally, measuring 14 mm in basal diameter and 4.2 mm in thickness. The mass was 8 mm from the foveola and 10 mm from the optic disc. Subretinal fluid was present surrounding the mass but not at the foveola. Notably, there was retinal invasion of the mass with mild, fresh, and chronic vitreous hemorrhage (Figure 1A). A dilated retinal arteriole feeding the tumor was slightly beaded (Figure 1B), and a venule draining the tumor, which was best observed on fluorescein angiography, was nondilated. OCT of the right eye confirmed the presence of CME, measuring 640 µm in central macular thickness (CMT; Figure 1C). B-scan ultrasonography demonstrated a somewhat echodense mass without extrascleral extension. These features were suggestive of choroidal melanoma with retinal invasion and remote CME.

The melanoma was treated with iodine-125 plaque radiotherapy. Intravitreal anti-VEGF therapy with bevacizumab (Avastin, Genentech) was administered at 1 month to reduce CME and subretinal fluid to improve visual acuity. During this visit, VA was steady at 20/200 OD. OCT demonstrated stable CME with a CMT of 660 µm, and tumor thickness was reduced from 4.2 mm to 3.8 mm. Monthly injections of bevacizumab until CME resolution was suggested.

## DISCUSSION

The most common etiologies of CME include post-cataract extraction; diabetic or hypertensive retinopathy; central or branch retinal vein occlusion; and post-radiation therapy.[5-7] Among intraocular tumors, there is a higher incidence of CME with retinal hemangioblastoma and vasoproliferative tumors than with uveal melanoma.[8]

A PubMed search for the key words “cystoid macular edema,” “melanoma,” and “choroid” revealed 11 published cases of CME secondary to choroidal melanoma.[4,5,9-13] The average age of affected individuals was 58 years (range 13-80 years). Like our patient, nine of the 11 patients were otherwise healthy with no medical comorbidities. One patient had diabetes mellitus and unrelated prior radium radiation treatment.[5] Another patient had a history of metastatic colon cancer.[11] Mean logMAR VA was 0.83 (20/134) and ranged from 20/20 to counting fingers on initial presentation. Seven cases showed signs of retinal detachment or retinal invasion. This may suggest that CME is more likely present in tumors that disrupt the retina.[4,5,9-13] Patients with a concurrent retinal detachment or retinal invasion also had poorer VA at initial presentation (logMAR of 1.09 [20/246]) compared with patients who did not (logMAR of 0.28 [20/38]). This is consistent with our patient, who demonstrated retinal invasion from choroidal melanoma with VA of 20/200 at initial presentation.

## CONCLUSION

Several mechanisms have been proposed for the pathogenesis of CME in eyes with choroidal melanoma. These include chronic retinal degeneration, chronic retinal pigment epithelium alterations, chronic retinal detachment, inflammation from tumor necrosis, and remote development of edema via intravitreal tumor-related factors.[4]

In our patient, we believe the retinal invasion from the underlying choroidal melanoma resulted in retinal disruption that possibly allowed for elevated VEGF levels in the vitreous cavity. However, in most cases, this rarely leads to CME remote from the tumor site. Further study is needed to determine whether VEGF levels in uveal melanoma with retinal invasion match or exceed VEGF levels in uveal melanoma without retinal invasion, as well as to elucidate the mechanism underlying this process. ■

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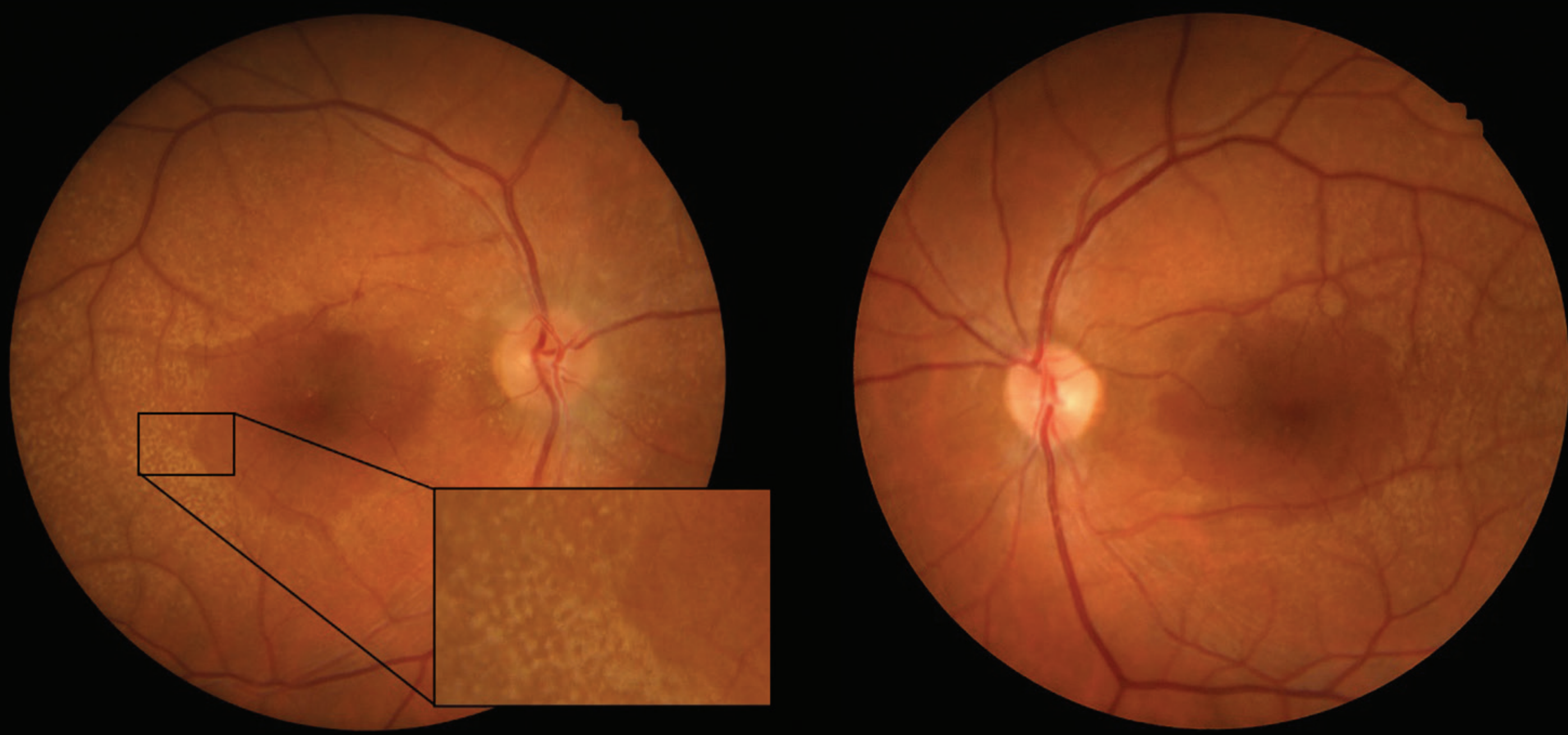
**ANKUR NAHAR, BS**
- Medical Student, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia
- ankur.nahar@students.jefferson.edu
- Financial disclosure: None

**AHMED SHEIKH, MD**
- Fellow, Mayo Clinic, Rochester, Minnesota
- ahmed90@gmail.com
- Financial disclosure: None

**CAROL L. SHIELDS, MD | SECTION EDITOR**
- Director, Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia
- Editorial Advisory Board Member, *Retina Today*
- carolshields@gmail.com
- Financial disclosure: None



# RETINAL FINDINGS IN ALPORT SYNDROME

An ocular examination can help track the impact of this rare genetic disease.

BY JOANA ROQUE, MD; JÚLIO ALMEIDA, MD; AND INÊS COUTINHO, MD

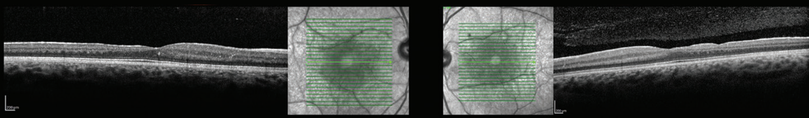
A 20-year-old White man was diagnosed with Alport syndrome during childhood in the context of a positive family history, sensorineural deafness, and progressive kidney dysfunction. The patient had been undergoing dialysis treatment for end-stage renal failure for 2 years when he presented to our clinic for his first routine ocular evaluation.

On examination, BCVA was 20/25 OU. Anterior segment examination was normal in each eye. The fundus examination of each eye revealed fovea-sparing retinal flecks, associated with the typical retinal 'lozenge' or 'dull macular reflex' (Main Figure). OCT showed symmetrical temporal macular thinning, which is also consistent with Alport syndrome (Figure, next page).

## DISCUSSION

Alport syndrome is a rare genetic disorder caused by abnormalities in the synthesis of type IV collagen. The typical presentation includes early-onset renal failure, hearing loss, and ocular abnormalities in up to 70% of patients. These abnormalities can involve the lens and cornea, but retinal changes are the most common ocular finding, particularly perimacular dot-and-fleck retinopathy. The dots and flecks can produce an abnormal tapetal-like reflex, and their demarcation from the perifoveal area results in a dull macular reflex or 'lozenge.'[1-4]

The macular flecks do not cause visual dysfunction, but they provide important information for the nephrologist because they indicate a more severe effect of the disease on



## TEMPORAL RETINAL THINNING IS ALSO VERY COMMON WITH ALPORT SYNDROME.

the kidneys. Temporal retinal thinning is also very common with Alport syndrome.

Overall, the visual prognosis of these patients is favorable; however, ophthalmic examination may play an important role in the diagnosis and in determining the severity of Alport syndrome,[5] especially in male patients with early-onset renal failure. ■

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**JÚLIO ALMEIDA, MD**
- Ophthalmology Resident, Hospital Prof. Doutor Fernando Fonseca, Lisbon, Portugal
- Financial disclosure: None

**INÊS COUTINHO, MD**
- Retina Specialist, Hospital Prof. Doutor Fernando Fonseca, Lisbon, Portugal
- Financial disclosure: None

**MANISH NAGPAL, MBBS, MS, FRCS | SECTION EDITOR**
- Senior Consultant, Retina and Vitreous Services, The Retina Foundation, Ahmedabad, India
- drmanishnagpal@yahoo.com
- Financial disclosure: Consultant (Nidek)

**JOANA ROQUE, MD**
- Ophthalmology Resident, Hospital Prof. Doutor Fernando Fonseca, Lisbon, Portugal
- joananunesroque@gmail.com
- Financial disclosure: None

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# MATTHEW A. CUNNINGHAM, MD

**When did you know you wanted to be a vitreoretinal specialist?**

I became interested in medicine during undergrad as an engineering major at the University of Miami. I was accepted into the accelerated BS/MD Junior Honors Medical Program at the University of Florida, and was intrigued by the pathophysiology seen in the ophthalmology clinic with my mentor, Sonal S. Tuli, MD.

I was not exposed to vitreoretinal surgery until my second year of residency, when I assisted with my first vitrectomy and membrane peel on a patient with a complex diabetic tractional retinal detachment. My attending took a complex-appearing situation and meticulously and skillfully peeled the membranes off the detached and damaged retina, allowing the detached retina to be anatomically repaired. At that moment, I knew that I wanted to be a vitreoretinal specialist.

Dr. Cunningham and his family at the 2021 Florida Retina Institute retreat in Orlando, Florida.

**I read that you have an interest in clinical trials. What about them interests you most?**

Clinical trials have played a pivotal role in establishing the standard-of-care treatment options we are able to offer patients in our clinics. I am most interested in how clinical trials help advance medical knowledge and help retina specialists improve patient care. By participating in trials, we potentially allow our patients to be the first to benefit from a novel treatment for their retinal condition.

Shortly after I joined the practice, I initiated the clinical research department at Florida Retina Institute. One of the more exciting trials we have participated in was the Kingfisher trial, which compared brolucizumab (Beovu, Novartis) with aflibercept (Eylea, Regeneron) for the treatment of diabetic macular edema. We continue to expand our research efforts and are actively enrolling in new studies. Benjamin J. Thomas, MD, has initiated our research efforts in Jacksonville, Florida, and continues the research mission.

**How do you juggle practicing at multiple locations and spending time with your family?**

A healthy work-life balance is critical in our specialty; it keeps us grounded and makes us better physicians. Spending quality time with my wife and daughters helps to keep things in perspective. I enjoy being outdoors biking, golfing, and coaching my daughter in soccer.

Four years after joining Florida Retina Institute, my partner, Elias Mavrofrides, MD, and I spearheaded an initiative for an annual company-wide retreat for the physicians and their families. Events like these allow us all the time to recharge and bring our families together.

**Back in 2018, you did an article for *Retina Today* about your work in Jamaica. Do you still travel there to provide eye care?**

During the past several years, the Eye Health Institute has partnered with the University of Michigan's Third Century Initiative to create a place for eye examinations and storage of equipment in rural areas. The initiative retrofitted a climate-controlled shipping container and shipped the pod to Jamaica. The initial pod was sent to Hanover, and we examined patients there during the mission trip.

I have not been able to participate in a mission trip since the pandemic started. However, I truly enjoy playing a role in the retinal care for the Jamaican population who do not have easy access to routine eye care.

In the future, I'd like to take part in vitreoretinal surgical mission trips for underserved populations. To make it a success, this requires integration with local Jamaican ophthalmologists. I have make some local connections with general ophthalmologists during previous trips, which I hope develop into partnerships. As COVID numbers start to improve, there have been talks of returning to Jamaica in 2022.

**What advice do you have for aspiring vitreoretinal specialists?**

1) Ensure that you have learned all of the fundamentals of general ophthalmology. As a retina specialist, you will be frequently asked about general ophthalmology topics that patients will expect you to answer.

2) Stay up to date with the literature. Management for various retinal conditions is everchanging with novel therapies and surgical techniques/devices.

3) Foster your relationships with mentors. Vitreoretinal surgery is humbling and having mentors to discuss challenging cases with is extremely helpful, especially during your first few years after fellowship. ■

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**MATTHEW A. CUNNINGHAM, MD**
- Vitreoretinal Surgeon, Florida Retina Institute, Orlando, Florida
- mcunningham@floridaretinainstitute.com
- Financial disclosure: Consultant (Alimera, Allergan, Novartis)


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C3 is where all three complement pathways converge, driving multiple damaging downstream effects—inflammation, opsonization, and formation of the membrane attack complex. All of this can lead to permanent retinal cell death in the pre-lesion, which is where your patients have the most to save.[2-9]
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