RT
Retina Today
JULY/AUGUST 2021 VOL. 16, NO. 5
RETINATODAY.COM

eyetube

RARE AND INHERITED RETINAL DISEASES

An Update on Clinical Trials and Treatment Advances

LET'S TALK ABOUT GENE THERAPY FOR INHERITED RETINAL DISEASES

THE INS AND OUTS OF GENETIC TESTING

THREE PEARLS FOR SURGERY IN UVEITIS PATIENTS

Geographic Atrophy | **Stargardt Disease** | **Inherited Retinal Diseases**

Learn more at IvericBio.com

Retina Today (ISSN 1942-1257) © 2021 Bryn Mawr Communications LLC is published January/February, March, April, May/June, July/August, September, October, and November/December by Bryn Mawr Communications LLC, 1008 Upper Gulph Road, Wayne, PA 19087. Subscription is free to all applicable US retina physicians. All others, applicable subscription charges apply. For subscription information call +1 800 492 1267 (US only) or e-mail retinatoday@bmctoday.com. Pending periodical postage paid at Wayne PA and additional entry offices. POSTMASTER Please send address changes to Bryn Mawr Communications LLC, 1008 Upper Gulph Road, Wayne, PA 19087. Bryn Mawr Communications LLC provides certain customer contact data, which may include customer names, addresses, phone numbers and e-mail addresses, to third parties for promotional and/or marketing purposes. If you do not wish Bryn Mawr Communications LLC to make your contact information available to third parties for any marketing purposes, please contact us at 800-492-1267 or e-mail us at retinatoday@bmctoday.com. This publication is intended for health care professionals and providers only. The information contained in this publication, including text, graphics and images, is for informational purposes only and is not intended to be a substitute for professional medical advice. Bryn Mawr Communications LLC, via its Editors and the Publisher, accepts no responsibility for any injury or damage to persons or property occasioned through the implementation of any ideas or use of any product described herein. While great care is taken by the Publisher and Editors to ensure that all information is accurate, it is recommended that readers seek independent verification of advice on drug or other product usage, surgical techniques and clinical processes prior to their use. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, the publication or the Editorial Board. References made in articles may indicate uses of medical equipment or drugs at dosages, for periods of time and in combinations not included in the current prescribing information. Inclusion of advertising material in this publication, or in supplements thereof, does not constitute any representation or guarantee by Bryn Mawr Communications LLC of the quality of such products or of the claims made by the manufacturers.

TABLE OF CONTENTS

Cover image credit: ©iStockphoto.com

RARE AND INHERITED RETINAL DISEASES

22 **Let's Talk About Gene Therapy for Inherited Retinal Diseases**
A discussion with Mark E. Pennesi, MD, PHD; Jacque L. Duncan, MD; Andreas Lauer, MD; Aaron Nagiel, MD, PHD; and Artur V. Cideciyan, PHD; Moderated by Allen C. Ho, MD

26 **The Ins and Outs of Genetic Testing for Inherited Retinal Diseases**
By Marc Mathias, MD

30 **AAV Gene Therapy Trials To Watch**
By Christine Kay, MD

34 **Tips and Tricks for Evaluating Children for Inherited Retinal Degenerations**
By David Xu, MD; Michael N. Cohen, MD; Michael A. Klufas, MD; and Jose S. Pulido, MD, MS, MBA, MPH

38 **Localized Steroid Therapy for Chronic Noninfectious Uveitis**
By Sumit Sharma, MD

42 **Three Pearls for Surgery in Uveitis Patients**
By Lisa Faia, MD

DEPARTMENTS

UP FRONT

6 **Medical Editors' Page**

9 **Retina News**

MEETING MINUTES

11 **Angiogenesis, Exudation, and Degeneration 2021–Virtual Edition**
An interview with David Sarraf, MD, and Philip J Rosenfeld, MD, PhD; By Matthew R. Starr, MD

13 **Live Meeting Roundup**

IMAGING

14 **Clinical Utility of OCT Angiography for AMD**
By Koosha Ramezani, MD; Hagar Khalid, MD; Luísa S.M. Mendonça, MD; and Nadia K. Waheed, MD, MPH

GLOBAL PERSPECTIVES

18 **Valsalva Retinopathy and Crossfit Training**
By Pedro Manuel Baptista, MD; Catarina Castro, MD; André Ferreira, MD; João Leite, MD; and Angelina Meireles, MD

SURGICAL PEARLS

44 **14 Tips for Scleral Suturing for Any IOL**
By William E. Smiddy, MD

MEDICAL RETINA

46 **A Rare Manifestation of Chronic Myelogenous Leukemia**
By Michael Weaver, DO; Samir Dalia, MD; and Heeral R. Shah, MD

OCULAR ONCOLOGY

50 **Uveal Melanoma Classified by The Cancer Genome Atlas**
By Zeynep Bas, MD, and Carol L. Shields, MD

CODING ADVISOR

54 **Action Steps to Effectively Manage Prior Authorization and Step Therapy Policies**
By Joy Woodke, COE, OCS, OCSR

VISUALLY SPEAKING

56 **Intravitreal Cysticercosis With Full Thickness Macular Hole**
By Vishal Agrawal, MD, FRCS

IN THE BACK

57 **Ad Index**

58 **5Q with Aaron Nagiel, MD, PHD**

WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

Detect Early. Treat Early.

ForeseeHome is a **remote monitoring** program for at-risk wet AMD fellow eyes that helps **detect conversion** at 20/40 or better in 83% of patients.[2]

- FDA Cleared
- Medicare Covered

ForeseeHOME™
AMD Monitoring Program

Introduce your patients to ForeseeHome during an injection visit and offer them an extra level of protection.

Our Diagnostic Clinic works with your staff to easily implement an "inject and protect" protocol into your practice workflow that requires minimal effort or additional time.

The Key to Successful Home Monitoring

NOTAL VISION DIAGNOSTIC CLINIC

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring
- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

NOTAL VISION™
Diagnostic Clinic

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.

See website for FDA Indication for Use.

SM-125.1

GET STARTED TODAY

1-855-600-3112

Mon-Fri, 8 AM to 6 PM EST

www.foreseehome.com/hcp

A THIRST FOR MORE


It's been almost 4 years since voretigene neparvovec (Luxturna, Spark) hit the market, and we are still talking about it as if we had found the Holy Grail. For many patients with Leber congenital amaurosis (LCA) caused by biallelic *RPE65* mutations, it's been a dream come true. The success stories simply melt your heart, especially those of pediatric patients who can do things they might never have been able to do without this gene therapy.

Now that we have had a small taste of victory, we want more, because treatment for inherited retinal diseases (IRDs) isn't possible with just one Holy Grail (as far as we know). The AAV vector worked for the *RPE65* gene; what else can it do? Perhaps it will prove successful in treatments for other forms of LCA, retinitis pigmentosa (RP), X-linked retinoschisis, choroideremia, and achromatopsia. Each of these diseases affects a small patient population, but if voretigene neparvovec taught us anything, it was that a successful gene therapy can be life-altering and well worth the winding journey through clinical investigation.

More than 30 trials are under way for various gene therapy candidates and delivery methods, including AAV vectors, lentivirus vectors, antisense oligonucleotides, CRISPR therapy, and optogenetics. We seem to get updates and new interim data constantly. Some are positive (a patient with RP regained some visual perception after treatment with gene therapy and training with specialized goggles), whereas others are less so (Biogen's investigation of timrepigene emparvovec for the treatment of choroideremia did not meet its primary efficacy endpoint at 12 months).[1,2]

But these findings are all positive, in the long run, because every trial is an opportunity to learn more about the genetic underpinnings of the disease in question, the transduction, the surgical technique, etc. What we see as a failed trial today will teach us something that will help to make the next trial a success tomorrow.

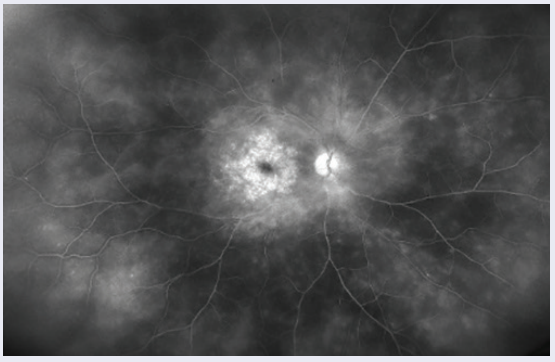
It's a lot to follow, and many of us are too busy caring for patients in the here and now to wade through the onslaught of phase 1/2 trials, 6-month interim data, and case reports. In this issue of *Retina Today*, we have boiled it down to what you really need to know. IRD experts share their thoughts on how the research is going, what to expect in the near future, and which trials are worth watching. Other leaders in the field provide pointers on evaluating patients for IRDs and how to order genetic testing.

We are learning volumes about IRDs and the mutations that cause them. With the help of genetic testing and gene registries we are better able to identify patients and help move research forward. But it takes a concerted effort by all of us to screen patients, order genetic testing, and recommend participation in appropriate clinical trials. Caring for patients with IRDs now involves far more than simply counseling them on what to expect as the disease progresses. It takes time to discuss the gene therapy candidates in the pipeline and why any given trial may—or may not—be right for each patient. But our IRD patients are hungry for information, and we should be just as eager to share it as they are to receive it. After all, we have the same goal: preserving vision. ■

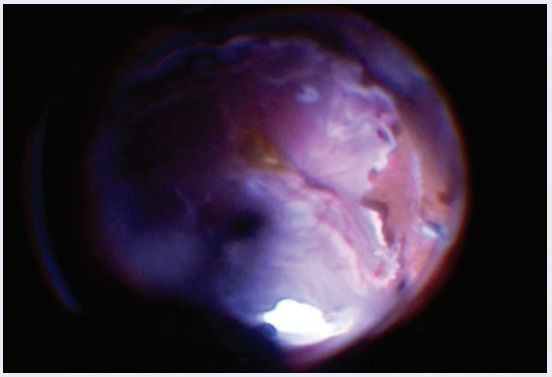
ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

ALSO IN THIS ISSUE:



Localized Steroid Therapy for Chronic Noninfectious Posterior Uveitis, page 38



Three Pearls for Surgery in Uveitis Patients, page 42

1. Sahel JA, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. Preprint. Posted online May 24, 2021. *Nat Med*.
2. Biogen announces topline results from phase 3 gene therapy study in choroideremia [press release]. Biogen. June 14, 2021. Accessed June 22, 2021. investors.biogen.com/news-releases/news-release-details/biogen-announces-topline-results-phase-3-gene-therapy-study

0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg:

- **Proven to reduce uveitis recurrence at 6 and 12 months[1]***
  [At 6 months–18% for YUTIQ and 79% for sham for study 1 and 22% for YUTIQ and 54% for sham for study 2 (*P*<.01). At 12 months–28% for YUTIQ and 86% for sham for study 1 and 33% for YUTIQ and 60% for sham for study 2.]
- **Innovative Durasert® technology is designed for a sustained release of fluocinolone acetonide for up to 36 months with just 1 YUTIQ implant[2]**

For more information, visit **YUTIQ.com**

J code: J7314

Now With a Siliconized Needle

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, phase 3 studies in adult patients (N=282) with noninfectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to noninfectious uveitis, or the use of prohibited medications.[1,3]

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

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.

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.

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.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Please see next page for Brief Summary of full Prescribing Information.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** EyePoint Pharmaceuticals Receives FDA Approval of YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg. Global Newswire. https://www.globenewswire.com/news-release/2018/10/15/1621023/0/en/EyePoint-Pharmaceuticals-Receives-FDA-Approval-of-YUTIQ-fluocinolone-acetonide-intravitreal-implant-0-18-mg.html. Accessed February 7, 2020. **3.** Data on file.

EyePoint PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472

02/2021
US-YUT-2100009

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%)

(continued)

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

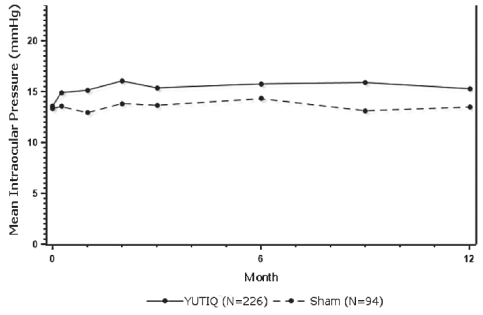
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
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%)

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%)

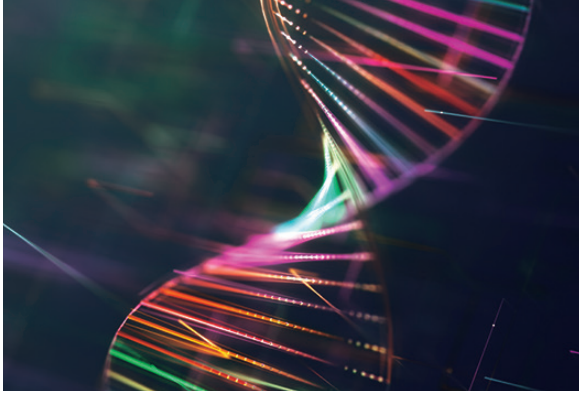
Figure 1: Mean IOP During the Studies



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.

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA
Patented.

JULY/AUGUST 2021
VOL. 16, NO. 5 | RETINATODAY.COM



FARICIMAB EXTENDED TIME BETWEEN DME TREATMENTS

In two phase 3 trials, the bispecific antibody faricimab (Genentech) allowed treatment intervals for patients with diabetic macular edema (DME) to be extended to as long as 16 weeks, according to data presented at the American Diabetes Association (ADA) Virtual Scientific Sessions in June. This is the first time this level of durability has been achieved in a phase 3 study in DME, according to Genentech.

In the two trials, YOSEMITE and RHINE, patients with DME were randomly assigned 1:1:1 to faricimab 6.0 mg every 8 weeks after six initial monthly doses; faricimab 6.0 mg per personalized treatment interval (PTI) after four monthly doses; or aflibercept 2.0 mg every 8 weeks after five monthly doses. In the PTI arm, dosing intervals were adjusted based on prespecified visual and anatomic criteria. Safety and efficacy were assessed through week 100.

The primary endpoint was mean change in BCVA at 1 year, averaged over weeks 48, 52, and 56. Secondary endpoints included changes in anatomic outcomes over time and the proportions of patients in the PTI arm receiving treatments every 4, 8, 12, or 16 weeks at 1 year.

Both studies met the primary endpoint and found that faricimab dosed every 8 weeks or by PTI demonstrated noninferior visual acuity gains compared with aflibercept every 8 weeks.

Faricimab was generally well tolerated, with no new safety signals identified. Safety endpoints in the trials included incidence and severity of adverse events.

Faricimab is the first treatment that targets two pathways, VEGF and angiopoietin-2, to control the growth of neovascularization, according to Genentech.

Some of this information was presented earlier this year at Angiogenesis, Exudation, and Degeneration 2021.

PDS FOR AMD: DATA SUBMITTED TO FDA FOR REVIEW

Genentech has submitted data on its Port Delivery System (PDS) for the treatment of AMD to the US FDA, the company announced in June. The FDA accepted the biologics license application under priority review, and a decision is expected in October, according to Genentech.

If approved, the PDS would be the first eye implant capable of providing continuous drug delivery to individuals with wet AMD as an alternative to frequent eye injections, potentially reducing treatment burden on patients, physicians, and health care systems, according to the manufacturer.

A survey from the phase 3 Archway study of the PDS found that 93.2% of patients reported preferring the PDS over intravitreal injections; the most common reported reasons were less discomfort and the need for fewer treatments.

The data submission to the FDA is based on positive results from preliminary analysis of the phase 3 Archway study, which showed that, of patients being treated with the PDS, more than 98% were able to go 6 months without needing additional treatment before refill. In addition, patients with the PDS achieved vision outcomes equivalent to patients receiving monthly ranibizumab intravitreal injections (Lucentis, Genentech). The PDS was generally well tolerated, with a favorable benefit-risk profile.

The ongoing Portal extension study is evaluating long-term safety and efficacy of the PDS in wet AMD. A marketing authorization application for the PDS has also been accepted by the European Medicines Agency and is under review.

The PDS is a permanent refillable eye implant designed to continuously release ranibizumab into the eye over time. The implant contains a customized formulation of ranibizumab not approved by the FDA, different from the ranibizumab intravitreal injection that is FDA-approved to treat wet AMD, diabetic retinopathy (DR), DME, and other retinal diseases.

PDS FOR DME AND DR: STUDY DESIGNS DETAILED

The PDS is also being evaluated in the treatment of DR with or without DME, according to a presentation by Margaret Chang, MD, at the ADA meeting. She described the design of two ongoing phase 3 trials, Pavilion and Pagoda, evaluating the use of PDS containing ranibizumab 100 mg/mL in these diabetic eye conditions.

Pavilion will evaluate the prophylactic effects of PDS with ranibizumab 100 mg/mL every 36 weeks versus clinical observation in patients with moderately severe to severe nonproliferative DR without DME.[1]

Pagoda will evaluate the tolerability of PDS filled with ranibizumab 100 mg/mL every 24 weeks and its efficacy compared with monthly intravitreal ranibizumab 0.5 mg injections in patients with DME.[2] Both trials will evaluate additional key endpoints including patient-reported outcomes. The trials will assess efficacy, safety, and tolerability of PDS and its potential to provide clinical benefits in DR and DME with reduced treatment burden.

Both the Pagoda and Pavilion trials are actively recruiting participants, according to Genentech.

1. A multicenter, randomized study in participants with diabetic retinopathy without center-involved diabetic macular edema to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the Port Delivery System relative to the comparator arm (PAVILION). Accessed July 8, 2021. clinicaltrials.gov/ct2/show/NCT04503551
2. This study will evaluate the efficacy, safety, and pharmacokinetics of the Port Delivery System with ranibizumab in participants with diabetic macular edema compared with intravitreal ranibizumab (Pagoda). Accessed July 8, 2021. clinicaltrials.gov/ct2/show/NCT04108156

COMPLEMENT REGULATOR SHOWED BIOLOGICAL ACTIVITY IN DRY AMD TRIAL

A recombinant human complement factor H (CFH) demonstrated biological activity to regulate complement in patients with geographic atrophy (GA) secondary to dry AMD, according to initial data from a phase 2a study. The ongoing ReGAtta trial of GEM103 (Gemini Therapeutics) found that the compound is well tolerated and demonstrates a differentiated safety profile with no increased risk of choroidal neovascularization and minimal inflammation, according to a June press release from the company.

ReGAtta is a multicenter open-label ascending-dose study designed to evaluate the safety and tolerability of GEM103 in genetically defined patients with GA secondary to dry AMD. Loss-of-function variants in the *CFH* gene have been confirmed in 55 of the 62 patients enrolled, according to Gemini.

In the trial, both 250-µg and 500-µg doses of GEM103 resulted in sustained elevated *CFH* levels from the first evaluated time point of 1 month (at least 6-fold and 12-fold above baseline, respectively). The levels then continued to increase in a dose-dependent manner. Changes in biomarkers of complement activation indicated that GEM103 has the ability to regulate the complement system and overall disease-related inflammation, consistent across all genotypes enrolled.

The compound was well tolerated, with no serious adverse events or early discontinuations related to the study drug and no serious ocular adverse events. The company is discussing with regulators the design of late-stage clinical trials.

PEPTIDES OF PEDF PROTECT RETINAL NEURONS

Peptide fragments formed from pigment epithelium-derived factor (PEDF) protect the retina's neuronal cells, and this natural protective mechanism of PEDF may have therapeutic implications, according to researchers at the National Eye Institute (NEI). Their findings were published online ahead of print in the *Journal of Neurochemistry*.[1]

The researchers evaluated the neurotrophic effects of PEDF and its fragments in an in vitro rat model of cultured primary retinal neurons that die spontaneously in the absence of trophic factors.

"Results show that PEDF protected photoreceptor precursors from apoptosis, preserved mitochondrial function, and promoted polarization of opsin, enhancing their developmental process, as well as induced neurite outgrowth in amacrine neurons," the study authors reported.

"PEDF may have a role for treating eye disease," said Patricia Becerra, PhD, senior author of the study and chief of the NEI Section on Protein Structure and Function, in a press release from the NEI. "If we want to exploit the protein for therapeutics, we need to separate out the regions responsible for its various properties and determine how each of them works."

The PEDF protein has functionally distinct domains, and researchers in the Becerra lab previously found that each domain can work independently. The team's model, which used animal cells, allowed them to identify the individual processes and mechanisms driving PEDF's protective effects, according to Germán Michelis, a graduate student and the study's first author, also quoted in the NEI press release.

"Our findings support the neurotrophic PEDF peptides as neuronal guardians for the retina, highlighting their potential as promoters of retinal differentiation and inhibitors of retina cell death and its blinding consequences," the study authors concluded. ■

1. Michelis G, German OL, Villasmil R, et al. Pigment epithelium-derived factor (PEDF) and derived peptides promote survival and differentiation of photoreceptors and induce neurite-outgrowth in amacrine neurons. Preprint. Published online June 16, 2021. *J Neurochem*.

ANGIOGENESIS, EXUDATION, AND DEGENERATION 2021—VIRTUAL EDITION

New findings around iRORA and cRORA.

AN INTERVIEW WITH DAVID SARRAF, MD, AND PHILIP J ROSENFELD, MD, PHD; BY MATTHEW R. STARR, MD

The Angiogenesis, Exudation, and Degeneration 2021—Virtual Edition meeting was packed with groundbreaking reports. Recently, the topic of identifying patients with lesions that could predict the development of geographic atrophy (GA) has attracted interest. Such lesions may prove to be biomarkers for clinical trials and evidence physicians can use to counsel patients on their long-term visual prognoses.

For this article, Matthew R. Starr, MD, a vitreoretinal fellow at Wills Eye Hospital, interviewed David Sarraf, MD, of UCLA Stein Eye Institute and Philip J. Rosenfeld, MD, PhD, of Bascom Palmer Eye Institute about their presentations at the 2021 Angiogenesis meeting. Both presenters detailed new findings on two types of lesions that may serve as useful GA biomarkers: incomplete retinal pigment epithelial (RPE) and outer retinal atrophy (iRORA) and complete RPE and outer retinal atrophy (cRORA).

MATTHEW R. STARR, MD: PLEASE BRIEFLY DESCRIBE THE IMPORTANCE OF DETECTING IRORA OR LESIONS PREDATING THE DEVELOPMENT OF IRORA.

David Sarraf, MD: OCT provides a more granular grading system of atrophy so that we can better identify earlier thresholds of intervention and prevention. Therapies in clinical trials for GA aim to reduce the rate of progression of disease. Targeting patients at earlier stages of intervention and aiming to reduce the development of end-stage GA and central blindness are critical because we cannot reverse this disease. OCT provides the opportunity to do this.

Philip J. Rosenfeld, MD, PhD: A group of retina providers are interested in identifying changes on OCT that predate GA. How you view fundus and en face images influences how you view that OCT. Depending on the type of OCT machine, some retina physicians rely on dense raster scans, maps, and en face imaging, whereas others rely on averaged B-scans.

The first notion of identifying these predictive lesions in nascent GA came in 2014 with a report by Robyn Guymer, AM, FAHMS, and colleagues in which they detailed changes within the outer plexiform layer and inner nuclear layer as well as hyporeflective wedge-shaped bands within the outer retina. Those authors, however, did not include hypertransmission defects in the choroid. We believe these defects indicate that the RPE is dying—but not dead yet.

Prof. Guymer's work led to the development of the Classification of Atrophy Meeting group. This consensus group eventually developed the belief that hypertransmission defects are important markers predating the development of cRORA. However, the notion of nascent GA does not take into account these hypertransmission defects, and thus iRORA is a more encompassing term. Detection of these lesions may allow better clinical guidance for patients who have yet to develop GA.

DR. STARR: DR. SARRAF, WHY WERE ONLY EXTRAFOVEAL LOCATION AND INTRARETINAL HYPERREFLECTIVE FOCI FOUND TO BE ASSOCIATED WITH PROGRESSION TO CRORA, WHEREAS OTHER STUDIES HAVE SHOWN FEATURES SUCH AS SUBRETINAL DRUSENOID DEPOSITS AND HYPOREFLECTIVE FOCI WITHIN THE DRUSEN CORE TO BE ASSOCIATED WITH LATE AMD DEVELOPMENT?

Dr. Sarraf: These may be the most important risk factors. Subretinal drusenoid deposits and hyporeflective foci are likely also important, but our study may not have been powered to show that.

DR. STARR: DR. ROSENFELD, DO TRANSIENT HYPERTRANSMISSION DEFECTS SEEN ON EN FACE OCT IMAGES CORRELATE WITH THE DEVELOPMENT OF GA, OR IS IT PRIMARILY PERSISTENT DEFECTS?

DETECTION OF THESE LESIONS MAY ALLOW BETTER CLINICAL GUIDANCE FOR PATIENTS WHO HAVE YET TO DEVELOP GA.

Dr. Rosenfeld: iRORA has a very high probability of leading to GA. Once iRORA is identified, GA will most likely develop within 1 to 2 years. Once you have this, you are beyond recovery and on the way to GA. The ability to identify hypertransmission defects larger than 250 µm and the significant association of these patients to develop cRORA indicates the clinical utility these lesions present for clinical trials and physicians.

DR. STARR: ARE THERE OTHER IMAGING MODALITIES THAT MAY PREDICT CRORA PROGRESSION?

Dr. Sarraf: iRORA and even milder subtypes of cRORA may not be detected with fundus autofluorescence (FAF) or fluorescein angiography, which supports OCT as perhaps the most granular classification system available. The OCT biomarkers may therefore be the best way to predict GA. Choroidal flow deficit analysis with OCT angiography has the potential to predict atrophy, and this was recently validated by the Sadda group at UCLA.

Dr. Rosenfeld: Hypertransmission defects precede any FAF findings. Once they are seen on FAF, it is GA. Until there is a dark spot on FAF, there is no GA. There are two large-scale studies—SWAGGER, evaluating swept-source imaging of GA, and IMPACT, evaluating the natural history of drusen—seeking to identify early multimodal imaging findings in patients without cRORA who later go on to develop GA and cRORA.

DR. STARR: DO YOU BELIEVE STUDIES NOW EVALUATING GA PROGRESSION MAY BE ABLE TO TARGET IRORA LESIONS AS WELL AND PERHAPS PREVENT OR SLOW CRORA DEVELOPMENT?

Dr. Rosenfeld: Hypertransmission defects lead to a 68% increase in the risk of developing GA compared with patients with intermediate AMD. This is extremely important for new clinical trials seeking to evaluate disease progression. Trials can use this in identifying how to slow the development of GA.

This concept of using hypertransmission defects on OCT will allow clinical trials to enroll patients without crossing the threshold of GA development and will allow studies to present earlier readouts of findings, perhaps at 6 or 12 months, to identify high-risk patients. Both of these metrics are useful in counseling patients and in designing clinical trials.

Dr. Sarraf: Yes, GA trials are now using iRORA and cRORA as thresholds for intervention and prevention. By preventing the development of cRORA, we may be able to better preserve central visual acuity as opposed to preventing GA, which may be a later, more end-stage outcome of atrophic AMD more commonly associated with central blindness.

DR. STARR: WHAT ARE THE NEXT STAGES IN EVALUATING IRORA LESIONS?

Dr. Sarraf: We are hoping to define subcategories of iRORA better to more precisely and accurately identify earlier and later stages of iRORA.

Dr. Rosenfeld: We hope to gather longer-term data, beyond 3 years, and further solidify hypertransmission defects on OCT as metrics for cRORA progression. ■

MATTHEW R. STARR, MD
- Assistant Professor of Ophthalmology, Mayo Clinic, Rochester, Minnesota
- mstarr1724@gmail.com
- Financial disclosure: None

DAVID SARRAF, MD
- Clinical Professor of Ophthalmology, Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles
- dsarraf@ucla.edu
- Financial disclosure: Advisory Board Member (Amgen, Genentech, Optovue); Consultant (Amgen Bayer Healthcare, Genentech, Novartis, Optovue, Iveric Bio); Investigator (Amgen, Genentech, Heidelberg, Optovue, Regeneron); Grants/Honoraria (Amgen, Bayer Healthcare, Genentech, Novartis, Optovue, Regeneron); Speaker (Bayer Healthcare, Novartis, Optovue); Equipment (Heidelberg, Optovue, Topcon); Stock Owner (Optovue)

PHILIP J. ROSENFELD, MD, PHD
- Professor of Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine, Miami
- Editorial Board Member, *Retina Today*
- prosenfeld@med.miami.edu
- Financial disclosure: Research Support (Carl Zeiss Meditec, Iveric Bio, Stealth BioTherapeutics); Consultant (Apellis, Bayer, Boehringer-Ingelheim, Carl Zeiss Meditec, Chengdu Kanghong Biotech, Ocunexus, Ocudyne, Regeneron, Unity Biotechnology); Equity Interest (Apellis, Ocudyne, Valitor, Verana Health)

LIVE MEETINGS ARE BACK!

It's time to pack your bags, hop on a flight, and treat yourself to some long-awaited in-person learning, lunching, and collegial fun. This fall, you can head to any number of live meetings across the United States and abroad. Here is a snapshot of upcoming retina events:

The Retina Society Annual Scientific Meeting

September 29 - October 2, 2021
Ritz Carlton, Chicago
www.retinasociety.org
Open to members and their guests only.
Visit www.retinasociety.org for membership information and application.

"We are so excited to see colleagues—in three dimensions—to share and discuss an outstanding scientific program and aggressive and fun social program. It's at the Ritz Carlton in Chicago, and it will be fabulous."

– Allen C. Ho, MD, President

ASRS Annual Scientific Meeting

October 8 - 12, 2021
JW Marriott San Antonio Hill Country Resort and Spa, San Antonio, Texas
www.asrs.org/annual-meeting

"Much of what we learn occurs during informal discussions outside of the scientific sessions. Our meeting will offer both structured and informal opportunities for debate, gossip, fist bumps, handshakes, and hugs. I hope attendees leave with fond memories of the Texas Hill Country, inspired by the scientific presentations, and energized by interactions with colleagues."

– Carl C. Awh, MD, President

AAO 2021

November 12 - 15, 2021
Retina Subspecialty Days, November 12 - 13
Ernest N. Morial Convention Center, New Orleans, Louisiana
www.aao.org/annual-meeting

"Attendees are finally going to feel some sense of normalcy as we reconnect with friends and colleagues we may not have seen for a long time. They will experience the energy and enthusiasm that can only come from live, in-person interactions."

– Srinivas R. Sadda, MD, Retina Subspecialty Day Program Co-Director

22nd Annual Retina Fellows Forum

December 3 - 4, 2021
The Westin Chicago River North, Chicago
mcpi.cvent.com/fellowsforum2021

FLORetina

December 16 - 19, 2021
Auditorium Parco della Musica Congress Center, Rome, Italy
floretina.com

CLINICAL UTILITY OF OCT ANGIOGRAPHY FOR AMD

In part 1 of this two-part series, the authors explore the advantages and disadvantages of this imaging modality.

BY KOOSHA RAMEZANI, MD; HAGAR KHALID, MD; LUÍSA S.M. MENDONÇA, MD; AND NADIA K. WAHEED, MD, MPH

OCT angiography (OCTA) is a new, rapid, noninvasive imaging modality. It uses motion contrast to visualize retinal and choroidal vasculature without the use of extrinsic dyes. OCTA images are obtained by decorrelating successive OCT B-scans acquired in the same area. Because the only change between successive OCT scans of the same retinal location should be due to the movement of blood through the vessels, OCTA software generates a map of the vasculature in the back of the eye.[1,2]

As a derivative of OCT, this new modality also delivers high-resolution, depth-resolved images (Figure 1), which is an advantage over fluorescein angiography (FA) and indocyanine green angiography (ICGA). The high resolution allows visualization of the microvasculature in much greater detail compared with dye-based angiography, potentially in a quantitative manner. Because of the depth resolution, individual vascular layers can be visualized independently.[1] These characteristics have quickly led OCTA to become vital in the evaluation of patients with several chorioretinal pathologies.

Two forms of OCTA are in use: spectral-domain (SD) and swept-source (SS) OCTA. An advantage of SS-OCTA over SD-OCTA is its faster scanning speed, which makes possible larger scan areas and denser scan patterns with comparable acquisition times. Additionally, SS-OCTA has less sensitivity roll-off with depth, and it typically uses a longer wavelength; these characteristics allow better visualization through opacities and visualization of deeper structures.[3,4]

In this report, we outline the clinical utility of OCTA in exudative and nonexudative AMD. In Part Two of this two-part series we will examine its usefulness for other retinal and choroidal vascular diseases.

OCTA IN AMD

AMD is the leading cause of vision loss in developed countries.[5] Severe vision loss in advanced AMD is associated with two conditions: geographic atrophy (GA) and macular neovascularization (MNV). OCTA has clinical utility in both the dry and wet forms of AMD.[6]

DRY AMD

In patients with dry AMD, the primary utility of OCTA is in identifying eyes that are phenotypically dry but that have underlying nonexudative neovascular disease. Nonexudative MNV has been described as type 1 neovascularization without exudative retinal changes. These lesions can be seen as staining plaques on ICGA. They display no leakage on FA or subretinal fluid on OCT.[7]

OCTA assists in the diagnosis of nonexudative MNV by identifying the presence of flow underneath the retinal pigment epithelium (RPE) and above Bruch membrane, in a flat irregular pigment epithelial detachment (PED; Figure 2).[7]

Roisman et al used a multimodal approach to follow 11 patients with intermediate nonexudative AMD in one eye and type 1 neovascular AMD in the fellow eye. Three of 11 patients showed a plaque lesion on ICGA correlating with subclinical MNV detected by OCTA.[8] Another study found that eyes with subclinical MNV have a higher risk of exudation after 1 year of follow-up compared with eyes without

detectable subclinical MNV at baseline. Although there is no evidence of benefit in treating these patients, they represent a higher-risk cohort that perhaps warrants closer follow-up.[9]

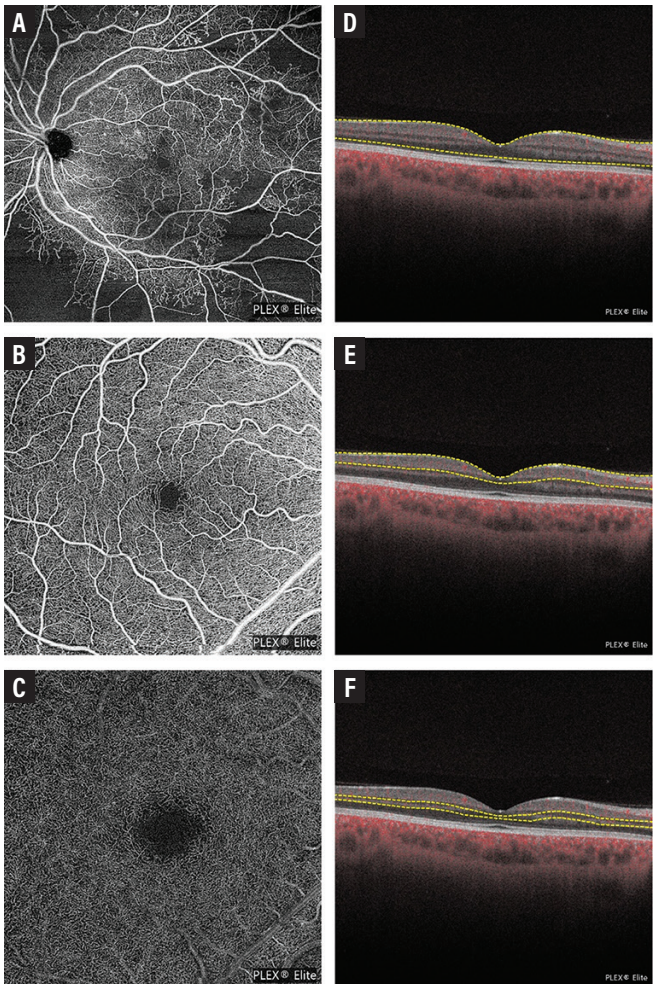


Figure 1. OCTA en face projections of full retinal depth (A), superficial retinal slab (B), and deep retinal slab (C), acquired in a healthy individual. Segmented B-scans with flow overlay corresponding with each en face image are shown on the right (D-F).

WET AMD

One of the most important applications of OCTA is in the detection of neovascularization in wet AMD.[4] En face OCTA images can be used to visualize vascularized networks, while their exact location in the retina is depicted by B-scans.[4,7]

MNV on OCTA has been described as a central trunk vessel with a peripheral capillary tuft, although this morphology is not applicable to all MNVs. Several other morphology terms have been proposed, many lacking validation.[10] Compared with FA, MNV lesions captured on OCTA tend to be smaller, probably due to better delineation of the neovascular complex margins on OCTA, which can be obscured by leakage on FA.[11]

The sensitivity and specificity of OCTA compared with FA and ICGA vary across studies, with a range of 50% to 100%.[12] It should be noted that published studies have used different devices, and some authors have included a mix of MNV subtypes.[12]

Shadowing due to hemorrhage and the presence of tall PEDs can increase the false negative rate. Combined application of OCTA and cross-sectional OCT has helped to improve sensitivity and specificity in detecting type 1 MNVs. The detection of type 3 MNV and polypoidal complexes seems to be more challenging on OCTA.[12]

Although OCTA can be used to monitor MNV lesion response to anti-VEGF treatment, studies on this topic have not been in full agreement. Whereas some authors reported a reduction in MNV size,[13] others found no change or even an increase in size after 1 to 2 weeks of maximal regression (Figure 3). It has also been demonstrated that, after anti-VEGF treatment, MNV may lose some of the fibrillary vessels at the edges.[1,4,14]

Care should be taken regarding common OCTA interpretation pitfalls that can arise from either image acquisition or processing. One such error occurs in the presence of GA and RPE disruption, causing enhanced signal penetration into the choroid. With concurrent loss of choriocapillaris, large choroidal vessels can be displaced upward and mimic an MNV

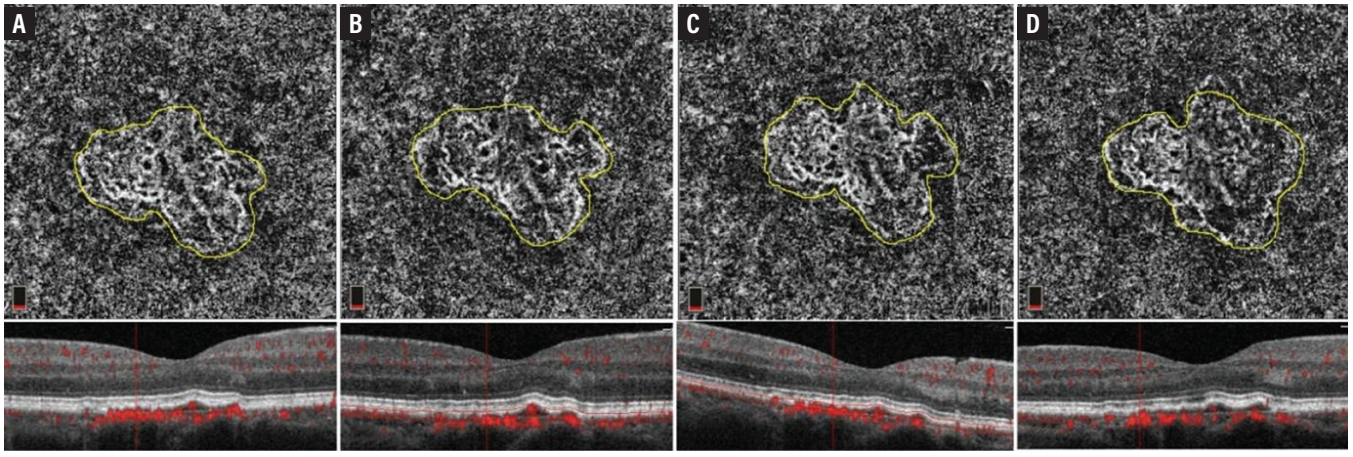


Figure 2. OCTA en face images (top row) and B-scans (bottom row) from an eye with nonexudative MNV: follow-up through 4 consecutive years (A-D). The MNV lesion area has increased in size from 1.445 mm^2 at baseline (A) to 1.620 mm^2 on the most recent visit (D).

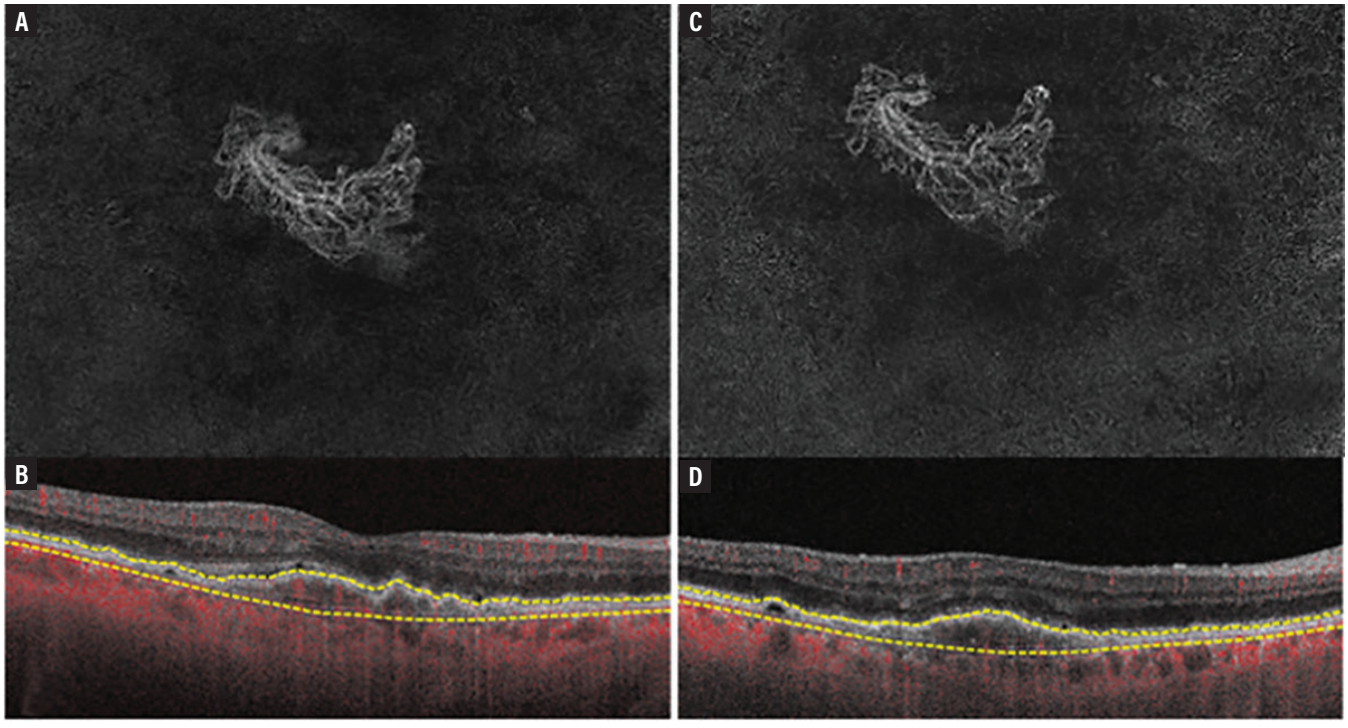


Figure 3. Morphologic aspect of MNV before and after treatment. The OCTA en face image (A) and B-scan (B) show the MNV lesion before injection. The OCTA en face image (C) and B-scan (D) show the MNV lesion 5 weeks after injection.

on en face OCTA. B-scan with and without flow overlay will show increased choroidal flow and signal hypertransmission, respectively, the latter of which is a notable characteristic of GA.[4]

Retinal pathologies can disrupt retinal layer detection, automated segmentation, and, consequently, the preset slabs. On these occasions, retinal slab segmentation should be performed manually to ensure correct detection of retinal boundaries.[4]

CONCLUSION

OCTA is a rapid, noninvasive imaging tool useful for a wide range of ophthalmic diseases in the clinical setting. However, limitations such as artifacts and segmentation errors can make scan interpretation challenging.[15] The inability to detect leakage is also a deficit compared with FA, limiting the clinical utility of OCTA. However, the higher resolution and the depth-resolved property of OCTA can add valuable information to clinical assessments of many conditions.[1] ■

1. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. *Prog Retin Eye Res*. 2018;64:1-55.
2. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitreous*. 2015;1:5.
3. Miller AR, Roisman L, Zhang Q, et al. Comparison Between Spectral-Domain and Swept-Source Optical Coherence Tomography Angiographic Imaging of Choroidal Neovascularization. *Invest Ophthalmol Vis Sci*. 2017;58(3):1499-1505.
4. Greig EC, Duker JS, Waheed NK. A practical guide to optical coherence tomography angiography interpretation. *Int J Retina Vitreous*. 2020;6(1):55.
5. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106-e116.
6. Chalam KV, Sambhav K. Optical Coherence Tomography Angiography in Retinal Diseases. *J Ophthalmic Vis Res*. 2016;11(1):84-92.
7. Querques G, Srour M, Massamba N, et al. Functional characterization and multimodal imaging of treatment-naive "quiescent" choroidal neovascularization. *Invest Ophthalmol Vis Sci*. 2013;54(10):6886-6892.
8. Roisman L, Zhang Q, Wang RK, et al. Optical Coherence Tomography Angiography of Asymptomatic Neovascularization in Intermediate Age-Related Macular Degeneration. *Ophthalmology*. 2016;123(6):1309-1319.
9. de Oliveira Dias JR, Zhang Q, Garcia JMB, et al. Natural History of Subclinical Neovascularization in Nonexudative Age-Related Macular Degeneration Using Swept-Source OCT Angiography. *Ophthalmology*. 2018;125(2):255-266.
10. Mendonça LSM, Perrott-Reynolds R, Schwartz R, et al. Deliberations of an International Panel of Experts on OCTA Nomenclature of nAMD [published online ahead of print, 2020 Dec 25]. *Ophthalmology*.
11. Costanzo E, Miere A, Querques G, Capuano V, Jung C, Souied EH. Type 1 Choroidal Neovascularization Lesion Size: Indocyanine Green Angiography Versus Optical Coherence Tomography Angiography. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT307-OCT313.
12. Perrott-Reynolds R, Cann R, Cronbach N, et al. The diagnostic accuracy of OCT angiography in naive and treated neovascular age-related macular degeneration: a review. *Eye (Lond)*. 2019;33(2):274-282.
13. Kuehlewein L, Sadda SR, Sarraf D. OCT angiography and sequential quantitative analysis of type 2 neovascularization after ranibizumab therapy. *Eye (Lond)*. 2015;29(7):932-935.
14. Amoroso F, Miere A, Semoun O, Jung C, Capuano V, Souied EH. Optical coherence tomography angiography reproducibility of lesion size measurements in neovascular age-related macular degeneration (AMD). *Br J Ophthalmol*. 2018;102(6):821-826.
15. Arya M, Sabrosa AS, Duker JS, Waheed NK. Choriocapillaris changes in dry age-related macular degeneration and geographic atrophy: a review. *Eye Vis (Lond)*. 2018;5:22. Published 2018 Sep 15.

HAGAR KHALID, MD
- Moorfields Eye Hospital, London
- Institute of Ophthalmology, University College London
- Ophthalmology Department, Tanta University, Tanta, Egypt
- Financial disclosure: None

LUÍSA S.M. MENDONÇA, MD
- Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil
- Financial disclosure: Consultant (Gyroscope Therapeutics)

KOOSHA RAMEZANI, MD
- Boston Image Reading Center, Boston
- kramezani@bostonimagereadingcenter.com
- Financial disclosure: None

NADIA K. WAHEED, MD, MPH
- New England Eye Center, Tufts Medical Center, Boston
- Financial disclosure: Consultant (Apellis, Nidek, Boehringer Ingelheim); Grants/Research Support (Carl Zeiss Meditec, Heidelberg, Nidek, Optovue, Topcon, Regeneron); Shareholder (Ocudyne); Office Holder (Gyroscope Therapeutics)

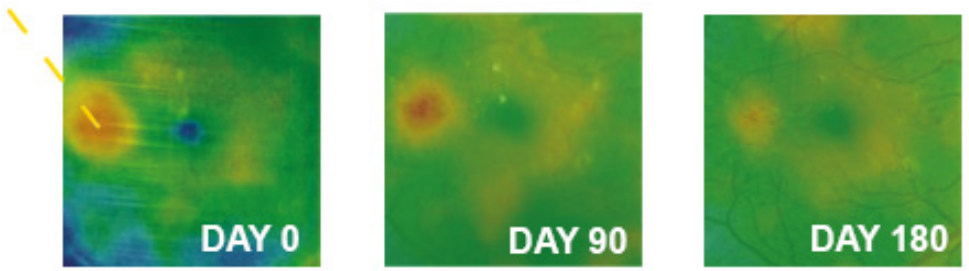
easyret®

577nm FIBER
TECHNOLOGY LASER

Enhance your subthreshold laser treatments thanks to the new Mosar® imaging system:

- Import patient's diagnosis images for treatment planning
- Perform subthreshold laser macular treatments thanks to Easyret® SubLiminal® mode
- Take pictures or record treatment videos to document your treatments
- Prepare and record advanced treatment reports including diagnosis images
- Improve your patient's follow-up

Subliminal® laser therapy is a tissue sparing treatment mode for the treatment of DME and CSC



DME treatment - Images courtesy of Alejandro Filloy Rius, MD. Ph.D – Tarragona Spain

Learn more
about clinical aspects on
www.subliminal-laser-therapy.com

CALL TODAY
855.767.5784

Headquarters:
Tel: +33 (0)4 73 745 745
contact@quantelmedical.fr

LEARN MORE:
www.quantel-medical.com

Quantel medical BY LUMIBIRD
ellex

VALSALVA RETINOPATHY AND CROSSFIT TRAINING

When and how to treat this rare entity in young, active people.

BY PEDRO MANUEL BAPTISTA, MD; CATARINA CASTRO, MD; ANDRÉ FERREIRA, MD; JOÃO LEITE, MD; PEDRO MENÉRES, MD; AND ANGELINA MEIRELES, MD

Valsalva hemorrhagic retinopathy (VR) is characterized typically by a sudden macular hemorrhage due to the rupture of superficial retinal capillaries after an acute increase in thoracic or abdominal pressure.[1,2] CrossFit training is a strength and conditioning workout comprising functional movements performed at a high intensity level and including forms of weightlifting. The movements mimic actions normally performed in daily life activities, and the Valsalva maneuver is included in most of the exercises. This article describes a case of VR related to CrossFit training.

CASE REPORT

A 42-year-old man was referred for emergency ophthalmic evaluation due to a sudden drop in visual acuity in the left eye after a CrossFit workout. On evaluation, the patient reported no history of personal or familial ophthalmic problems. No familial systemic medical history was reported, but the patient noted a history of systemic hypertension diagnosed at 32 years of age and well controlled since then with one beta-blocking agent (bisoprolol, 5 mg once daily).

On ophthalmic examination, BCVA was 20/20 OD and hand motion OS. No defects were found in the oculomotor examination or biomicroscopy. There was no relative afferent pupillary defect. Systemic blood pressure was 127/74 mm Hg.

On mydriatic fundoscopy, no alteration was found in the right eye. A macular retinal hemorrhage was seen in the left eye at the superotemporal arcade, with a suspected preretinal component within a gravitational tract including and hiding the inferior temporal arcade. Also noted were four other smaller intraretinal hemorrhages symmetrically positioned in each of the four vascular arcades. The retina was fully attached 360°, and no other alterations were found, including on the optic disc, apart from mild vascular tortuosity and mild fundus tessellation. Vitreous hemorrhage was absent (Figure 1).

The spectral-domain OCT (SD-OCT) revealed no alterations in the right eye and what appeared to be a detached inner limiting membrane (ILM) in the left eye at the foveal region, with a hyperreflective area compatible with blood within the sub-ILM space and with posterior shadowing.

Because the clinical picture was unchanged 1 week later, the patient was scheduled for pars plana vitrectomy (PPV). In the OR, the sub-ILM localization was confirmed as the major component of the hemorrhage. Posterior hyaloid detachment and careful ILM peeling were performed after the injection of brilliant blue G dye.

One month after the procedure, the patient's VA had improved to 20/20 OS. Fundoscopy revealed the absorption of the smaller hemorrhages and the absence of blood within the macular area, with no new findings. Macular SD-OCT

AT A GLANCE

- Valsalva retinopathy (VR) is a rare, typically unilateral preretinal hemorrhagic retinopathy secondary to a sudden increase in intrathoracic or intraabdominal pressure.
- VR occurs as a sudden and dramatic loss of vision due to the premacular location of the hemorrhage.
- The authors report a case of VR occurring in association with CrossFit training, an exercise regimen that makes use of the Valsalva maneuver.

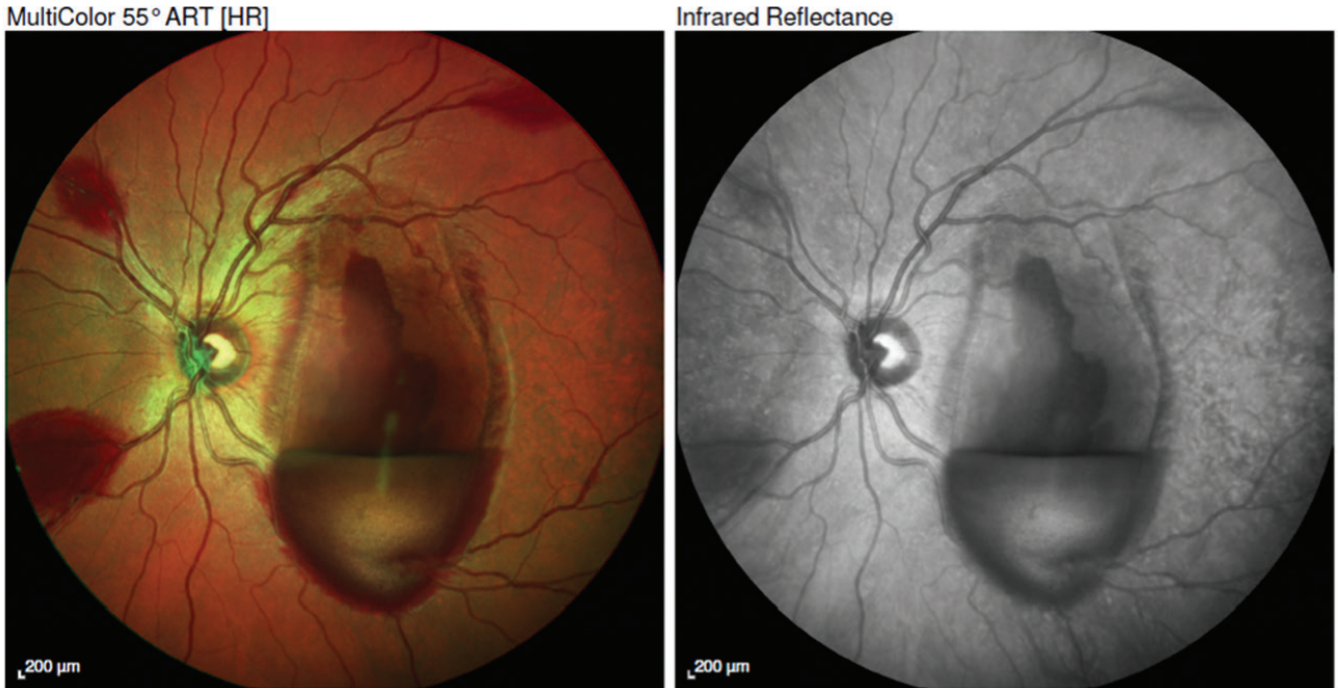


Figure 1. Fundus photography at presentation, left eye.

revealed no alterations in the right eye (Figure 2). In the left, a patent foveal depression was seen, with rare intraretinal hyperreflective dots and without signs of internal or external retinal or vitreoretinal interface alterations (Figure 3).

DISCUSSION

The first report of VR was made by Duane in 1972. The entity was described as typically a unilateral (rarely bilateral) preretinal hemorrhagic retinopathy secondary to a sudden increase in intrathoracic or intraabdominal pressure.[1] This stimulus leads to an increase in intraocular venous pressure, causing superficial retinal capillaries to rupture.[2] VR occurs as a sudden and dramatic loss of vision due to the premacular location of the hemorrhage. The patient whose case is reported here had the typical unilateral acute sudden loss in vision.

VR has been reported after Valsalva maneuvers associated with several activities, including vomiting, sexual activity or weightlifting during late pregnancy, constipation, playing musical wind instruments, colonoscopy, and dental procedures.[3] Valsalva maneuvers increase trunk rigidity and spine stability,[4] which is required in several CrossFit exercises. However, to the best of our knowledge there are no reports in the literature about a specific association of VR and CrossFit training, as in the case presented here.

Poorly controlled hypertension can lead to target-organ damage in several systems, including the cerebrovascular, cardiovascular, renal, and retinal systems.[5] Elevated blood pressure leads to vessel damage, giving rise to hypertensive retinopathy. One of the earliest findings is a diffuse narrowing of retinal arterioles,[6] which can persist despite proper antihypertensive treatment. Although chronic hypertensive retinopathy rarely causes significant visual loss, it can be a risk factor for VR.[7]

In the case presented here, the patient was diagnosed with hypertension early in life. Although in our evaluation his arterial pressure was within the normal range with medication, and only mild tortuosity was seen on fundoscopic examination, this cannot be neglected as a possible contributing factor to the patient's VR.

Observation is the standard treatment for VR, as in most cases it resolves spontaneously without compromising visual acuity.[8] However, even a small hemorrhage may take months to clear and can significantly reduce a patient's quality of life. Thus, early intervention is required both in the event of vitreous hemorrhage precluding proper retinal evaluation and in patients demonstrating a low rate of absorption or massive bleeding at the macula, particularly with subretinal or sub-ILM components.[7]

For large sub-ILM or subhyaloid hemorrhages obscuring the macula, membranotomy with Nd:YAG laser (pulsed/Q switched/1064 nm/frequency-doubled) treatment can be attempted within the first 3 weeks.[3] The treatment should be applied at the inferior margin of the hemorrhage, avoiding the fovea and large retinal vessels. Although good long-term results have been reported,[3] there are some risks, including formation of epiretinal membrane, retinal detachment, or iatrogenic retinal lesions.[9] Additionally, the risk of retinal

toxicity from contact with hemoglobin and other blood agents, namely by the sub-ILM component,[10] should not be neglected. Treatment with vitrectomy has been shown to result in significant and immediate visual improvement, preventing blood-related complications in these cases.[10]

OUTCOME AND CONCLUSION

In the case presented here, despite the absence of vitreous hemorrhage and the patient's young age, the treatment chosen was early intervention with PPV, due to the amount of blood with low probability of complete spontaneous reabsorption and the aforementioned risk of retinal toxicity. The patient achieved complete resolution of the macular hemorrhage and excellent functional outcome by 1 month after surgery.

VR is a rare entity that can lead to sudden and severe vision loss in young, active people. Systemic hypertension screening in the general population is mandatory, and control of hypertension is important to prevent damage to retinal vessels.

Despite its health benefits, CrossFit training presents some risks to ocular structures that cannot be neglected. To the best of our knowledge, this is the first report of a VR occurring specifically in association with CrossFit training. In selected cases of VR, after proper consideration of the components of the presentation, early PPV should be the option of choice. ■

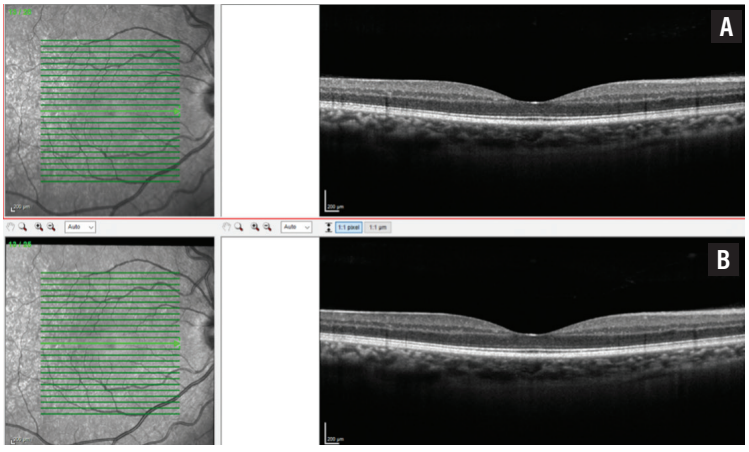


Figure 2. Macular SD-OCT at presentation (A) and at the end of follow-up (B), right eye.

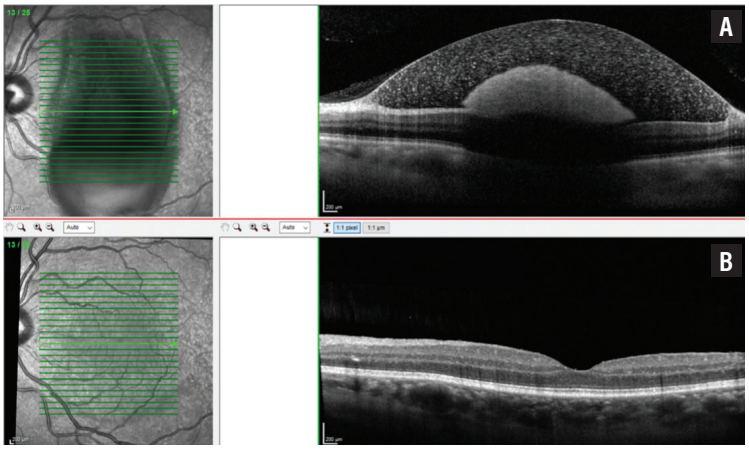


Figure 3. Macular SD-OCT at presentation (A) and at the end of follow-up (B), left eye.

1. Duane TD. Valsalva hemorrhagic retinopathy. *Trans Am Ophthalmol Soc*. 1972;70:298-313.
2. Mukherjee C, Kumar A, Mitra A. Valsalva maculopathy: To treat or not to treat. *Oman J Ophthalmol*. 2018;11(1):78-81.
3. Durukan AH, Kerimoglu H, Erdurman C, Demirel A, Karagul S. Long-term results of Nd:YAG laser treatment for premacular subhyaloid haemorrhage owing to Valsalva retinopathy. *Eye (Lond)*. 2008;22(2):214-218.
4. Hackett DA, Chow CM. The Valsalva maneuver: its effect on intra-abdominal pressure and safety issues during resistance exercise. *J Strength Cond Res*. 2013;27(8):2338-2345.
5. Kabedi NN, Mwanza JC, Lepira FB, Kayembe TK, Kayembe DL. Hypertensive retinopathy and its association with cardiovascular, renal and cerebrovascular morbidity in Congolese patients. *Cardiovasc J Afr*. 2014;25(5):228-232.
6. Fraser-Bell S, Symes R, Vaze A. Hypertensive eye disease: a review. *Clin Exp Ophthalmol*. 2017;45(1):45-53.
7. Simakurthy S, Tripathy K. Valsalva Retinopathy. In: StatPearls. StatPearls Publishing; February 14, 2021.
8. García Fernández M, Navarro JC, Castaño CG. Long-term evolution of Valsalva retinopathy: a case series. *J Med Case Rep*. 2012;6:346.
9. Byparedy R, Chawla R, Azad SV, Takkar B. Iatrogenic parafoveal macular hole following Nd-YAG posterior hyaloidotomy for premacular haemorrhage. *BMJ Case Rep*. 2016;2016:bcr2016217234.
10. De Maeyer K, Van Ginderdeuren R, Postelmans L, Stalmans P, Van Calster J. Sub-inner limiting membrane haemorrhage: causes and treatment with vitrectomy. *Br J Ophthalmol*. 2007;91(7):869-872.

PEDRO MANUEL BAPTISTA, MD
- Ophthalmology department, Centro Hospitalar e Universitário do Porto, Portugal
- Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal
- pedroyybaptista@gmail.com
- Financial disclosure: None

CATARINA CASTRO, MD
- Ophthalmology department, Centro Hospitalar e Universitário do Porto, Portugal
- Financial disclosure: None

ANDRÉ FERREIRA, MD
- Ophthalmology department, Centro Hospitalar e Universitário do Porto, Portugal
- Unit of Anatomy, Department of Biomedicine, Faculdade de Medicina da Universidade do Porto, Portugal
- Financial disclosure: None

JOÃO LEITE, MD
- Ophthalmology department, Centro Hospitalar e Universitário do Porto, Portugal
- Financial disclosure: None

ANGELINA MEIRELES, MD
- Ophthalmology department, Centro Hospitalar e Universitário do Porto, Portugal
- Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal
- Financial disclosure: None

PEDRO MENÉRES, MD
- Ophthalmology department, Centro Hospitalar e Universitário do Porto, Portugal
- Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal
- Financial disclosure: None

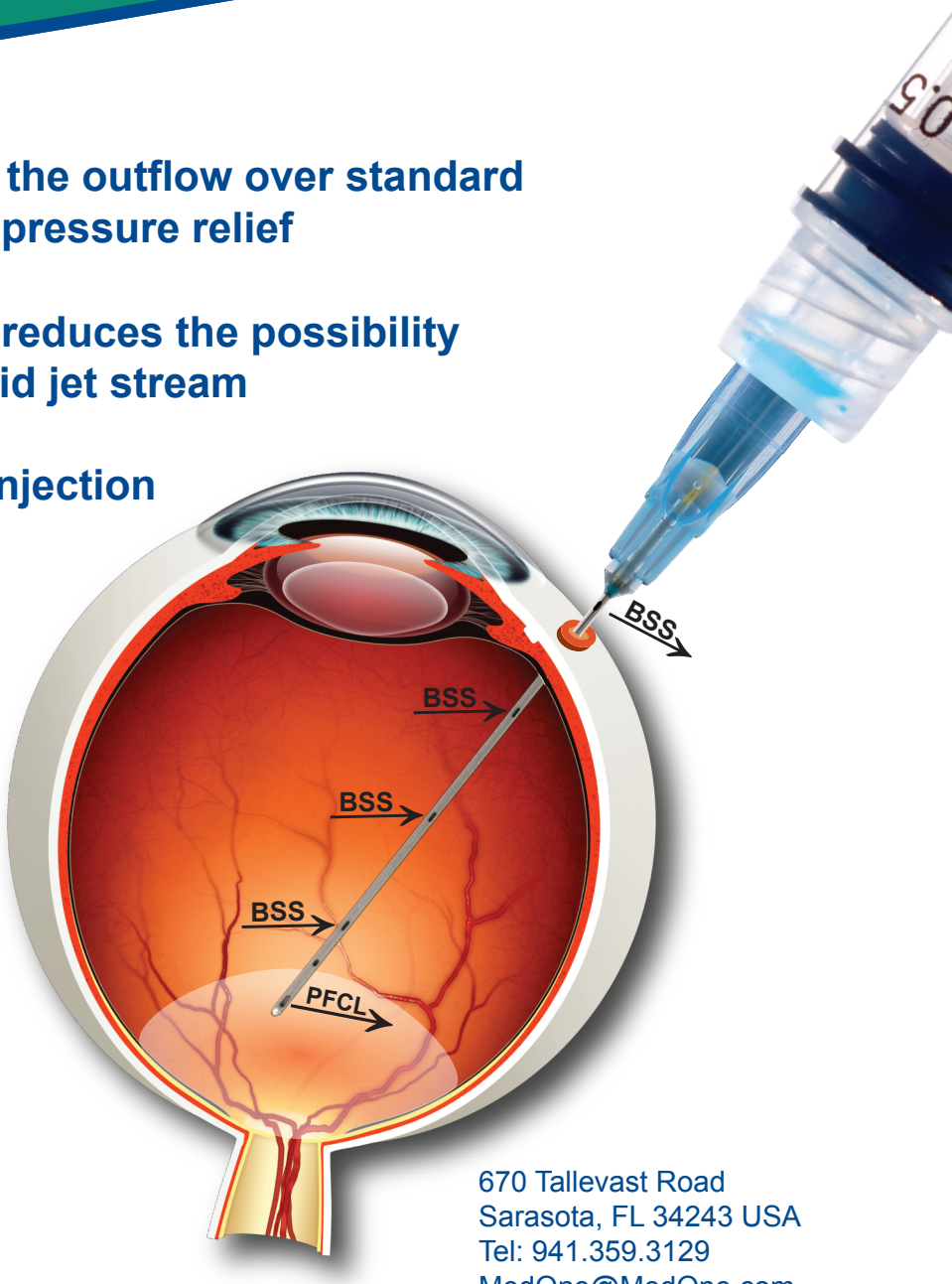
Works Best Under Pressure!

DualBore SideFlō® Cannulas

Optimized for simultaneous relief of pressure during injection of surgical liquids such as perfluorocarbon or staining dye in small gauge surgery.

- **Multiple egress vents double the outflow over standard DualBore cannulas for faster pressure relief**
- **Innovative side-port delivery reduces the possibility of retinal injury caused by fluid jet stream**
- **Maintains stable IOP during injection**
- **Available in 23g, 25g & 27g**

Patent #9937300



MedOne®

www.medone.com

670 Tallevast Road
Sarasota, FL 34243 USA
Tel: 941.359.3129
MedOne@MedOne.com

Let's Talk About Gene Therapy for Inherited Retinal Diseases

The approval of the first gene therapy in the United States has sparked significant interest in this patient population. What's next in the research pipeline?

A DISCUSSION WITH MARK E. PENNESI, MD, PHD; JACQUE L. DUNCAN, MD; ANDREAS LAUER, MD; AARON NAGIEL, MD, PHD; AND ARTUR V. CIDECIYAN, PHD
MODERATED BY ALLEN C. HO, MD

Allen C. Ho, MD: It has been almost 4 years since the approval of the first-in-human gene therapy, the first and only pharmacologic treatment for an inherited retinal disease (IRD), and the first AAV vector therapy approved in the United States: voretigene neparvovec (Luxturna, Spark) for Leber congenital amaurosis (LCA) caused by biallelic *RPE65* mutations. But our other patients with IRDs are counting the days to the approval of the next therapy.

DR. HO: WHAT DO WE NEED TO KNOW ABOUT SPARK'S THERAPY? WHAT'S YOUR EXPERIENCE NOW THAT WE ARE SEVERAL YEARS PAST APPROVAL? WHAT ABOUT THE RECENT PUBLICATION SHOWING PERIFOVEAL ATROPHY IN A SUBSET OF PATIENTS?

Mark Pennesi, MD, PhD: Treatment with voretigene neparvovec remains one of the great accomplishments in the field of IRDs. We have treated approximately 15 patients at our site, and we've seen some phenomenal results. We now have 5-year data from the original trials showing continued improvement and durability in those patients. The recent study on perifoveal atrophy is something that we need to take seriously and explore.[1] That was a retrospective study of a subset of centers, and we need to look at the entire set of treated patients—likely several hundred patients around the world—to understand the frequency of this event.

AT A GLANCE

- More than 30 clinical trials for inherited retinal diseases are in the works, including ones for Leber congenital amaurosis, retinitis pigmentosa, choroideremia, and achromatopsia.
- Real-world experience with voretigene neparvovec (Luxturna, Spark) has been very positive to date at multiple centers.
- With inherited retinal diseases, there is a general tendency to lose photoreceptors over time. The progression tends to show an inferior perimacular distribution, with relative retention in the foveal and superotemporal macula.
- Surgeons should be deliberate about where they place the bleb during subretinal gene therapy, balancing considerations of ease of detachment with remaining photoreceptor cells and iatrogenic damage to the fovea.

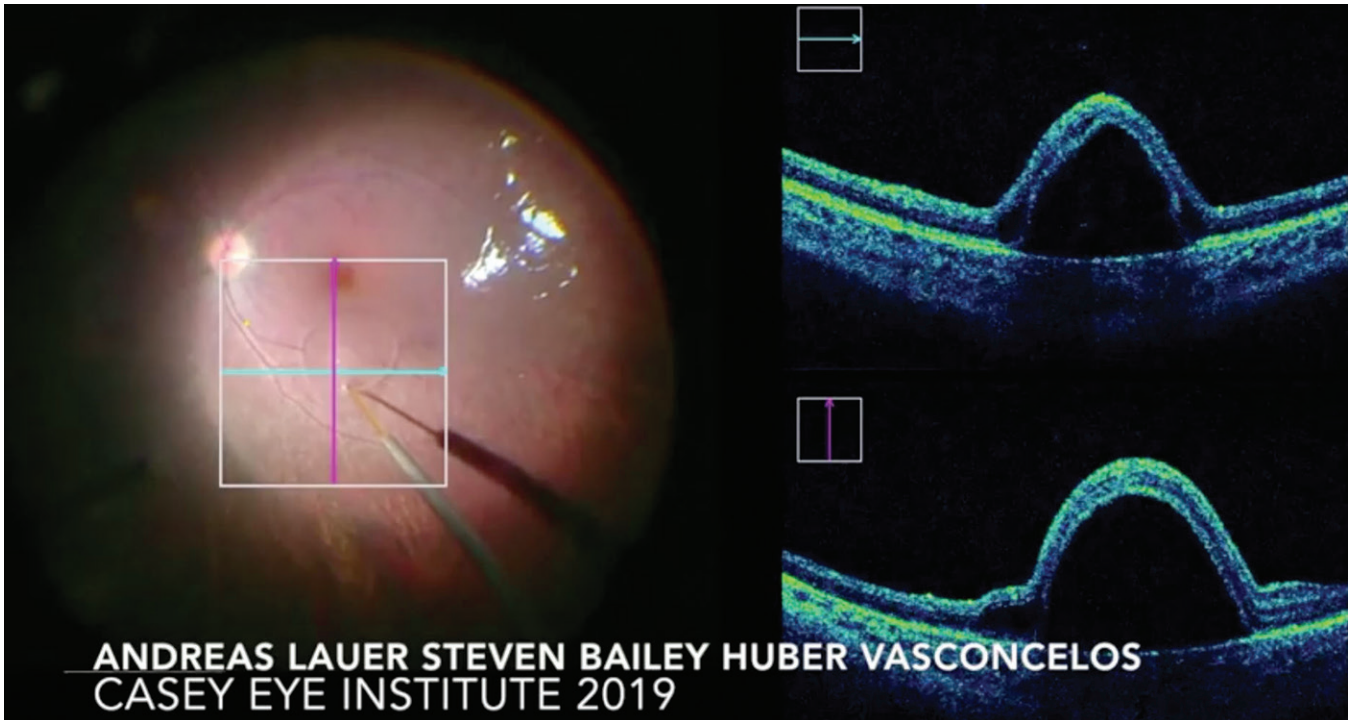


Image courtesy of Andreas Lauer, MD, Steven Bailey, MD, and Huber Vasconcelos, MD

Figure. During subretinal delivery, intraoperative OCT can help the surgeon place the needle properly when creating the bleb and titrate the speed of delivery.

Aaron Nagiel, MD, PhD: We've treated 23 patients at our site, and all of them have done well, especially the children. Those who are between 4 and 10 years of age have seemed to improve remarkably, and the stories that parents tell us about what the kids can do after surgery compared with before are heartwarming. The adults with more advanced disease may not benefit as much, but there is the hope that we can maintain the vision they have, and they all seem happy with their decision to have the surgery.

Artur V. Cideciyan, PhD: The natural history of the disease is quite variable in the sense that some young patients have lost a lot of photoreceptors early in their lives, whereas others retain photoreceptors. But independent of where the stage of disease is when the patient is first seen in the clinic, there is a general tendency to lose photoreceptors over time. The progression tends to show an inferior perimacular distribution, with relative retention in the foveal and superotemporal macula. Whether the recent findings are due to the gene therapy or the natural history of the disease needs to be evaluated further. However, chorioretinal atrophy spatially corresponding to the treatment area and occurring in a matter of months appears to be too fast compared with the slow natural history.

DR. HO: CURRENTLY, VORETIGENE NEPARVOVEC IS DELIVERED SURGICALLY ONLY AT SPECIFIC CENTERS. IF WE GET GENE THERAPIES FOR MORE COMMON DISEASES, WILL SUBRETINAL DELIVERY BE IN THE TOOLBOX FOR ALL RETINA SURGEONS?

Dr. Nagiel: Before we treated our first patients with voretigene neparvovec, we all performed hands-on training in live animals. That made sense for the administration of this novel therapy, particularly in young children. But if gene therapy becomes available for common retinal diseases, this delivery method should expand to all retina surgeons. Many, if not all, retina surgeons already have experience with subretinal tissue plasminogen activator delivery. Something as simple as an educational video and contact information of surgeons who participated in the trials should be enough to prepare surgeons to perform these procedures.

DR. HO: WHAT ARE SOME OF YOUR TIPS AND TRICKS FOR SUBRETINAL DELIVERY?

Andreas Lauer, MD: I've realized that you don't have to go fast to create a bleb. Now that I inject more slowly with less pressure, I feel that the anatomic recovery has been better. Also, there's immense value in preoperative planning and carefully looking at the anatomic and functional diagnostic tests. In our center, we look at images to pinpoint the target zone and decide where we think the patient will get the best benefit. You should be deliberate about where you place the bleb, and, once in the OR, you need to be delicate, calm, and ready to minimize any complications.

Dr. Nagiel: There is some nuance to how much pressure to apply onto the retina with the cannula. That's probably one of the most important factors, in combination with the injection pressure. We've migrated to using the Microdose

Injection Kit (MedOne), which has improved our delivery by allowing full surgeon control of the injection pressure. It allows you to titrate and get that sweet spot of pressure on the retina plus injection pressure to get the bleb to elevate.

I agree that presurgical planning of the target is important. Originally, I thought that the more peripheral or thinner atrophic areas aren't ideal to start a bleb, but those are usually the easiest places to get the bleb to rise, rather than closer into the macula where the retina is thicker.

Dr. Ho: The tools and the systems have improved, and the collective experiences are going to help all of us improve consistency of surgical delivery. There's a real difference in the ease of elevating the neurosensory retina using the MedOne syringe system and a 41-gauge cannula. Creating subretinal blebs in younger patients is more challenging than the older AMD patients in whom we are also exploring ocular biofactory gene therapy.

In younger patients, we double check with triamcinolone particles to ensure a posterior vitreous detachment and no residual cortical gel; we also bevel the cannula to create an angle, and we use intraoperative OCT in some cases. I never thought I needed it, but I like using it to get the cross-sectional real-time view to make sure the hyaloid is up.

DR. HO: IS INTRAOPERATIVE OCT REQUISITE FOR SUBRETINAL GENE THERAPY DELIVERY?

Dr. Lauer: Using intraoperative OCT is like using a backup camera to park a car. I'm better at parking when I use other views, and that same concept applies during surgery; the additional view helps me see morphologic changes when creating a subretinal bleb (Figure). One of the morphologic changes I look for is how the tissues respond when the needle is compressed against the retina and the choroid. It helps me understand the depth of the needle and when to start initiating a bleb. Once the subretinal space is created, I know I can continue to propagate that bleb. I should see—both axially with the microscope and in cross-section with the OCT—the growth of the bleb. This helps me understand that the needle is not in the suprachoroidal space or the choroid or creating retinoschisis.

It's also helpful when monitoring for foveal inversion. The fovea is usually concave and, if the injection is going a bit too fast, the fovea inverts. In that event, intraoperative OCT helps the surgeon titrate the speed of delivery. So intraoperative OCT is a useful tool, as it helps refine the surgery and reduces the risk of complication.

DR. HO: WHAT ARE SOME OF THE OTHER GENE THERAPIES IN THE PIPELINE FOR PATIENTS WITH IRDS?

Jacque L. Duncan, MD: There are more than 30 clinical trials in the works, including gene replacement trials for conditions such as *RPGR*-associated X-linked retinitis pigmentosa (RP), choroideremia, and achromatopsia associated with *CNGA3* and *CNGB3*. There are clinical trials under way for *CEP290*, a common cause of LCA or early onset retinal degeneration, and for *USH2A*, a common cause of either Usher syndrome type 2 or autosomal recessive RP.

There are many others in the planning stages, and innovative approaches are being used for genes that are too big to fit within the AAV delivery virus used with the *RPE65* gene. There are ways of skipping over certain mutations with fragments of RNA called antisense oligonucleotides.

Exciting advances are happening with CRISPR-Cas9 for patients with certain *CEP290* mutations, and this is the first time CRISPR-Cas9 is being delivered to modify DNA in situ.

For patients who don't know their genetic mutation, there are also mutation-independent treatments (eg, antioxidants, neurotrophic factors, or the delivery of stem cells) being developed that are meant to prolong the survival of photoreceptors and improve vision.

For patients with advanced vision loss, there are trials using optogenetics, prosthetics, and stem cells. There's a lot in development, and there will be even more in the future.

DR. HO: WHAT ARE THE MOST PROMISING STRATEGIES FOR SPECIFIC DISEASES?

Dr. Cideciyan: If the goal of the therapy is to improve vision, IRDs with the greatest promise are those in which patients have lots of photoreceptors and relatively little visual function. For those patients, we can try to molecularly intervene to improve function. One gene therapy target showing promise is the *CEP290* form of LCA. Another similar disease is retinal ciliopathy with *NPHP5* mutations that cause LCA. Fascinating results were shown in a canine model, and human therapies are hopefully on the horizon.

But if the goal of the treatment is to arrest photoreceptor degeneration and stop the loss of vision, then IRDs with a steady but slow progression have the greatest promise, such as the RP class of diseases.

What I find most challenging is the dual goal of simultaneously improving vision and slowing progression. For example, we recently evaluated autosomal-dominant RP patients and, to our surprise, there was not only the expected progression but also an unexpected level of dysfunction. This means that successful gene-specific interventions might be those able to improve vision in the short term and arrest progression in the long term.

Dr. Ho: Gene therapies have come a long way since they came to a standstill in 1999 at the University of Pennsylvania with Jesse Gelsinger, an 18-year-old patient who underwent systemic infusion of a gene replacement for ornithine transcarbamylase deficiency that caused a fulminant systemic inflammation and led to his death. We are still seeing some issues of inflammation.

DR. HO: HOW SHOULD WE BE HANDLING INFLAMMATION IN PATIENTS RECEIVING GENE THERAPY?

Dr. Pennesi: Inflammation is a crucial topic, and we have seen inflammation in almost every gene therapy program to some extent. The best way to treat inflammation is to prevent it from happening, and we are strong proponents of prophylactic steroids, often both oral and topical. But we need more basic science studies to understand what is causing the inflammation. There's still debate as to what components of the vector bring about an inflammatory response and why some patients have no response whereas others show robust responses.

DR. HO: GIVEN THE RISK OF INFLAMMATION, HOW LONG SHOULD WE FOLLOW PATIENTS FOR EFFICACY AND SAFETY PARAMETERS?

Dr. Cideciyan: If there is inflammation, it often presents within the first month; however, any of the effects that could potentially change the rate of degeneration long term might not be apparent for years. In IRDs, neurons die slowly, and we can look at the death rate with adaptive optics or OCT and determine over many years whether the rate of change of photoreceptor loss is changing due to treatment. In the *RPE65* trial, we monitored patients for more than 3 years and determined that there was neither arrest nor acceleration of photoreceptor loss. Thus, areas that showed clear treatment effect degenerated at the same rate as the natural history. With this kind of approach, we should be following patients for 2 to 5 years, minimum, in all clinical trials.

DR. HO: WHAT CHALLENGES ARE LIMITING THE DEVELOPMENT OF GENE THERAPIES FOR IRD PATIENTS?

Dr. Duncan: Myriad genetic mutations can cause retinal degeneration, many of which aren't very common. Thus, it's not necessarily feasible for a company to develop a gene-specific treatment for every gene that can cause disease in small numbers of patients.

Other challenges include how to deliver the therapy without causing inflammation or potentially detaching the retina. The photoreceptors may be so delicate that even detaching them for a short period of time with subretinal delivery may not be safe. Still, giving the therapy intravitreally may cause more inflammation and complications.

It's hard to know for sure exactly what's happening until you monitor for a long time, and that has been a significant challenge, leading us to develop more sensitive outcome measures to monitor how photoreceptors are faring, both functionally and structurally.

The field is rallying around the fact that we've seen some success. The *RPE65* story has inspired a lot of interest in the field and motivated people to work collaboratively, so that we can identify greater numbers of patients who might benefit from these types of therapies and participate in trials. We've learned a tremendous amount about the genetic causes of disease, yet 30% to 40% of patients still don't know what genes are to blame for their IRDs.

DR. HO: IS THERE AN IDEAL WAY TO ORDER A MOLECULAR TEST TO BETTER IDENTIFY THESE PATIENTS?

Dr. Nagiel: There are many options now, including free tests, and it can be challenging to know which one to choose. They aren't the same, and the panels are constantly changing. For example, the free ID Your IRD panel (Invitae) omits the *RPGR* gene and mitochondrial genes, whereas those genes are included in the free Foundation Fighting Blindness My Retina Tracker program. The ID Your IRD panel does include some rare IRD genes and genes for albinism not included in others. One might think whole exome sequencing would provide complete coverage, but sometimes this strategy can miss large deletions and duplications and deep intronic variants.

Thus, you can choose whichever large panel you prefer, but you should know the limitations of the tests in the context of your patient's findings. For example, if you're concerned about X-linked RP, you may not want to go with the ID Your IRD program.

Dr. Pennesi: Genetic testing is a snapshot in time, and it's a probability. I always explain to my patients that it's like fishing. If you don't catch a fish, that doesn't mean there aren't fish in the pond. It means that you didn't catch a fish. A negative result from genetic testing is not necessarily meaningful, especially if it was done several years ago. It might be worthwhile to test again because the technology continues to improve.

Dr. Duncan: I recently saw a young patient who used ID Your IRD and was told he had no mutations. However, it certainly looks like he has X-linked RP, so we have been working with the company to test only the *RPGR* gene. And never underestimate the value of working with genetic counselors, because they understand the nuances of how to interpret the variants of uncertain significance.

Continuing to monitor patients and remaining in contact with them is very valuable. It can be demoralizing for them to get an inconclusive result, and it's not unrealistic to suggest to them that the result could be different in the future.

Dr. Ho: Gene therapy is science fact right now, not science fiction. But it's not a reality for enough people, and this whole ecosystem of collaboration among organizations, surgeons, translational scientists, investors, and industry is a model for other afflictions beyond vision. Your leadership and careful approaches are much appreciated. ■

1. Gange WS, Sisk RA, Besirli CG, et al. Perifoveal chorioretinal atrophy after subretinal voretigene neparvovec-rzyl for RPE65-mediated Leber congenital amaurosis. *Ophthalmol Retina*. 2021;S2468-6530(21):00106-8.

(Continued on page 28)

The Ins and Outs of Genetic Testing for Inherited Retinal Diseases

The more you know about a patient's genetic status, the better equipped you are to recommend clinical trials.

BY MARC MATHIAS, MD

Inherited retinal diseases (IRDs) are frequently diagnosed in early childhood, creating the potential for early intervention to correct the underlying genetic cause of disease and protect or improve patients' vision in the long term. Until recently, there were no disease-modifying treatments for any IRD. As a result, genetic testing to determine the specific mutation that causes a patient's IRD has not been broadly used. The landscape changed nearly 4 years ago, however, with the first FDA approval of a gene therapy for an IRD—Leber congenital amaurosis (LCA) due to mutations in the *RPE65* gene.

This approval and the myriad clinical trials currently under way for other gene therapies have created a practical rationale for empowering patients to learn about their genetic status. As the field of IRD gene therapy continues to expand and progress, multiple stakeholders—including the eye health community, the biopharmaceutical industry, nonprofit organizations, and patients and their families—all have roles to play in realizing the potential benefits of intervention early in the disease process.

THE BENEFITS OF GENETIC TESTING

Given that many IRDs are progressive, early diagnosis and genetic assessment may help enhance patients' ability to improve their long-term vision outcomes. Therefore, it is important to educate pediatric patients and their families about the availability and potential benefits of genetic testing as soon as an IRD diagnosis has been made or, for those already diagnosed, at the patients' next visit.

Historically, genetic testing for IRDs has not been covered by health insurance because the results did not impact clinical practice or long-term prognosis. Recently, nonprofit organizations and industry leaders have come together to provide free testing for patients with an IRD diagnosis.

The Foundation Fighting Blindness My Retina Tracker program provides free testing for patients enrolled in the registry by their physician.[1] The genetic testing panel available through this program currently evaluates

AT A GLANCE

- Several nonprofit organizations and industry leaders have come together to provide free genetic testing programs for patients with an inherited retinal disease (IRD) diagnosis, including The Foundation Fighting Blindness My Retina Tracker program and the ID Your IRD program, developed in collaboration with Invitae.
- Patients and their parents must understand their genetic status to make informed decisions about clinical trial opportunities and participation.
- IRD gene registries can help researchers gain a better understanding of the heterogeneity of IRDs and the prevalence of different diseases and gene mutations.

285 IRD-associated genes, including mitochondrial DNA testing. To perform the test, a genetic sample is collected using a simple blood draw or saliva sample done in the physician's office or the patient's home. The genetic sample, informed consent, and requisition for testing are returned to Blueprint Genetics, the Foundation's industry testing partner, via a prepaid mailer.

The ID Your IRD program, developed in collaboration with Invitae, also offers free genetic testing for patients with a suspected IRD.[2] This test evaluates 293 IRD-associated genes but does not currently include the *RPGR* gene associated with X-linked retinitis pigmentosa (XLRP, Figure 1). The test offered through ID Your IRD has enrollment, sample collection, and result processes similar to those for My Retina Tracker.

Testing with either program can be ordered by any eye care provider for patients diagnosed with a covered IRD.

The genes evaluated in each panel are updated periodically, so patients with an IRD that is not currently included in a panel may be included in the future.

It is essential for patients and their parents to understand their genetic status to make informed decisions about clinical trial opportunities and participation. As new therapies hopefully gain approval in coming years, genetic status information will also help patients and parents learn which treatments might be appropriate for them.

GENETIC COUNSELING ESSENTIALS

Genetic testing is only the first step for patients with an IRD to become informed about their genetic status and related implications for clinical trial participation and therapeutic decisions. Genetic counseling is an essential component of genetic testing, and it is recommended that a genetic counselor be identified prior to undergoing testing to ensure that patients have access to an appropriate resource to help them understand their test results and discuss potential next steps.

In addition to answering questions about results, genetic counselors with expertise in IRDs may also be able to provide patients with information on relevant ongoing clinical trials. They also are well positioned to discuss potential IRD risks for parents who are considering having additional children.

Fortunately, with the expansion of molecular and precision medicine, there is a variety of resources available that can help connect IRD patients with a knowledgeable genetic counselor.

Some physician practices may have a genetic counselor on staff, whereas others may have a referral network of genetic counselors outside of their offices. Additionally, telephone-based genetic counseling is provided for free through both the My Retina Tracker and ID Your IRD programs.

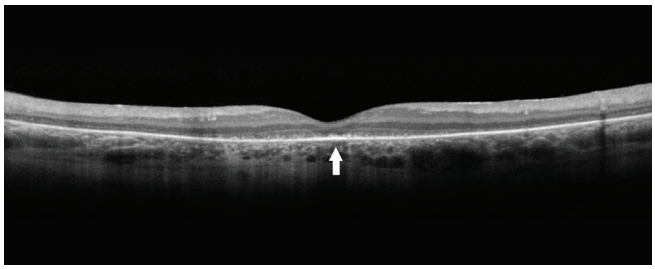


Figure 1. If a patient presents with signs suspicious for XLRP, as seen here, genetic testing may help confirm the diagnosis. The ID Your IRD panel does not include the *RPGR* gene; consider using the My Retina Tracker program instead.

IRD GENE REGISTRIES

Registries are essential resources to obtain insight into the natural history of specific IRDs and to collect information on the impact of different interventions (both disease-modifying and supportive) on patients' experiences and ability to perform daily activities.

The My Retina Tracker registry is designed to achieve several objectives that will expand the collective understanding of IRDs and how to treat them.[3] These objectives include gaining a better understanding of the heterogeneity of IRDs and the prevalence of the different diseases and gene mutations, assisting with the establishment of genotype-phenotype relationships, and improving the understanding of the natural history of specific IRDs.

Early diagnosis in the pediatric population provides an opportunity to better understand the natural history of early disease stages, when intervention may have more impact. Insights gained from analyzing registry data may accelerate research and development of clinical trials for treatments, and it may also provide a mechanism that facilitates more rapid recruitment for research studies and clinical trials.

My Retina Tracker collects data across an array of IRDs, but other IRD-specific registries and natural history studies are also available. For example, ProgStar is evaluating the natural history of Stargardt disease due to biallelic *ABCA4* mutations.[4] Other registries exist for several IRDs, including choroideremia, Usher syndrome (USH Trust), *CRB1*-related LCA/retinitis pigmentosa (RP), and blue cone monochromacy.

Patients who choose to particiate in these registries can make valuable contributions to our collective understanding of IRDs, and they may benefit by being notified when any clinical trial appropriate for their specific genetic mutation becomes available.

LIMITED TRIAL OPPORTUNITIES

There are more than 30 gene therapy clinical trials ongoing for diverse IRD indications, including XLRP, achromatopsia, LCA, RP due to a variety of genes, and others. Many of these trials, however, are open only to patients 18 years of age or older. Even fewer trials are open to children younger than 10, who may be the most likely to benefit from

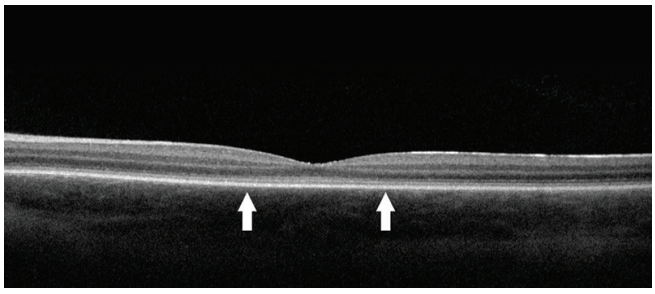


Figure 2. Certain pediatric patients with *CNGA3*- or *CNGB3*-associated achromatopsia may be eligible to enroll in clinical trials evaluating gene therapy.

therapies that can prevent damage to or loss of retinal cells.

Although patient safety must always be paramount in drug development, pediatric patients should be included in IRD gene therapy trials as soon as favorable safety profiles have been established because of the potential benefit of visual function preservation.

Pediatric participation in IRD clinical trials is also essential for understanding the impact of investigational therapies at earlier stages of disease, when benefit may be greatest, and for generating robust clinical data that allow patients, parents, and physicians to make informed decisions about therapeutic options that are ultimately approved. Pediatric patients are currently being recruited for clinical trials evaluating gene therapy for XLRP and for *CNGA3*- or *CNGB3*-associated achromatopsia (Figure 2).

COLLABORATING FOR IMPROVED OUTCOMES

The IRD gene therapy landscape is evolving rapidly, making it challenging to stay informed on the latest advances, especially those available to pediatric patients. Pediatric ophthalmologists, pediatric retina specialists, and genetic counselors who specialize in IRDs are valuable resources, as are many academic eye institutions.

Retina specialists should encourage patients to undergo IRD genetic testing and place a testing order if the patient with a suspected IRD is amenable. Advancing disease-modifying therapies for IRDs and giving pediatric patients new opportunities to preserve or improve their vision are communal responsibilities, and we can better achieve these important goals when we work together. ■

1. Foundation Fighting Blindness. My Retina Tracker Registry. Accessed June 4, 2021. www.fightingblindness.org/my-retina-tracker-registry
2. Invitae. ID Your IRD. Accessed June 4, 2021. www.invitae.com/en/idyourird
3. Inherited Retinal Degenerative Disease Registry (MRTR). Accessed June 4, 2021. clinicaltrials.gov/ct2/show/NCT02435940
4. Collison FT, Lee W, Fishman GA, et al. Clinical characterization of Stargardt disease patients with the p.N1868I ABCA4 mutation. *Retina*. 2019;39(12):2311-2325.

MARC MATHIAS, MD
- Assistant Professor, Ophthalmology, University of Colorado School of Medicine, Aurora, Colorado
- Financial disclosure: Research Support (ProQR Therapeutics, 4DMT Molecular Therapeutics, Alkeus Pharmaceuticals)

(Continued from page 25)

ARTUR V. CIDECIYAN, PHD
- Research Professor of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia
- cideciya@pennmedicine.upenn.edu
- Financial disclosure: Consultant/Grant Funding (ProQR Therapeutics, Atsena, Iveric Bio, PYC Therapeutics)

JACQUE L. DUNCAN, MD
- Professor of Clinical Ophthalmology; Inherited Retinal Degeneration Specialist; Academic Director, Retina Service; Vice Chair, Clinical Trials, Department of Ophthalmology, University of California San Francisco
- jacque.duncan@ucsf.edu
- Financial disclosure: Consultant (4D Therapeutics, AGTC, Astellas, Biogen, DTx Therapeutics, Editas, Eloxx, Eyevensys, Gyroscope, Horama, ProQR, Spark Therapeutics, Sparing Vision, Vedere); Funding (Acucela, Allergan/Abbvie, Biogen/Nightstar, Foundation Fighting Blindness, Neurotech USA, Second Sight Medical Products)

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

ANDREAS LAUER, MD
- Vitreoretinal Surgeon; Thiele-Petti Endowed Chair and Professor, Department of Ophthalmology, Casey Eye Institute, Oregon Health & Science University, Portland, Oregon
- lauera@ohsu.edu
- Financial disclosure: Consultant/Grant Funding (AGTC, Atsena, California Institute of Regenerative Medicine, Cambridge Consulting, Editas, Genentech, Iveric Bio, Oxford BioMedica, Biogen/Nightstar, Regenxbio, ReNeuron)

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)

MARK PENNESI, MD, PHD
- Associate Professor of Ophthalmology; Kenneth C. Swan Endowed Professor; Chief, Paul H. Casey Ophthalmic Genetics Division, Casey Eye Institute, Oregon Health & Science University, Portland, Oregon
- pennesim@ohsu.edu
- Financial disclosure: Consultant/Funding (4D Molecular Therapeutics, Adverum, Akous, AGTC, Astellas Pharmaceuticals, Atsena, Biogen/Nightstar, Blue Rock, DTx Therapeutics, Editas, Endogena, Eyevensys, Foundation Fighting Blindness, Gensight, Horama, Iveric Bio, Nayan, Nacuity Pharmaceuticals, Novartis, Ocugen, Ora, ProQR, PYC Therapeutics, Regenexbio, Roche, Sanofi, Sparing Vision, Viewpoint Therapeutics, Vedere)

BVI

Unrivalled Experience

*This Device is Only Available in Europe

Vitreq
Vitreoretinal Surgical Products

CryoTreq
Ophthalmic Cryo-Surgery

Unique | Straightforward | Compelling

- First and Only Single-Use, stand-alone device for ophthalmic cryosurgery
- Only seconds required for activation to reach cryogenic temperatures(1)
- Up to 15 freezing cycles per surgery

bvimedical.com

1) References CryoTreQ Technical File STED 2.2.4 "Performance Specifications: In a water bath at a temperature of 37 °C, an ice ball will be formed with a layer thickness of 0.8 mm within 6 seconds".

AAV Gene Therapy Trials To Watch

Here's what you need to know about the many gene therapies under investigation for inherited retinal diseases.

BY CHRISTINE KAY, MD

Many clinical gene replacement trials are under way for inherited retinal diseases (IRDs). Other than voretigene neparvovec (Luxturna, Spark), most IRD gene therapy trials are still in phase 1 or 2 with significant work remaining to be done (Table). This article provides an overview of ongoing ocular gene therapy trials to help retina specialists provide patients with educated and up-to-date counseling regarding their possible candidacy for clinical trials (Figure).

TRIALS TO WATCH

Retinitis Pigmentosa

AAV-RPGR (MeiraGTx/Janssen) is being evaluated for treatment of *RPGR*-associated X-linked retinitis pigmentosa (XLRP). Researchers have reported interim results of the phase 1/2 MGT009 clinical trial.[1,2] At 9 months, six of seven patients in the low and intermediate dose cohorts demonstrated improved or stable retinal sensitivity in the treated eye compared with baseline. Based on a vision-guided mobility maze, five of six patients demonstrated improvement in walk time for the treated eye at 9 months compared with baseline.

The low and intermediate doses are being evaluated in an ongoing expansion portion of the phase 1/2 study, which completed enrollment in the first half of 2020. The companies are planning a phase 3 pivotal study.

rAAV2tYF-GRK1-RPGR (AGTC-501, AGTC) for *RPGR*-associated XLRP is being investigated in a phase 1/2 trial. Enrollment is complete, with 28 patients assigned to one of six dose groups.[3,4] Data from all 28 patients have demonstrated a favorable safety profile. At 12 months, two of eight patients in groups 2 and 4 showed measurable improvements in visual sensitivity.

Interim 12-month data for groups 5 and 6 show a 50% response rate for patients who met the inclusion criteria for the phase 1/2 expansion trial and the phase 2/3 trials (at least a 7 dB improvement in at least five loci).[3]

4D Therapeutics is investigating the safety and tolerability of **4D-125** for the treatment of XLRP. The phase 1/2 trial is recruiting up to nine male patients with XLRP and assignging them to one of two dose levels. Patients will be followed for 24 months for safety, with secondary endpoints evaluating efficacy measures at 12 months.[5]

A phase 1/2 trial of **AAV2/5-hPDE6B (HORA-001, Horama)** for the treatment of retinitis pigmentosa (RP) associated with the *PDE6B* gene is under way in France.[6]

AT A GLANCE

- One ocular gene therapy has been FDA-approved, and the large number of ongoing trials brings hope to IRD patients who are waiting for a potential treatment.
- With standard augmentation gene therapy, novel optogenetic therapies, and other advances such as antisense oligonucleotide therapy, retina specialists must remain up to date to provide the best possible care for their patients.

TABLE. CLINICAL IRD GENE THERAPY TRIALS

Adeno-Associated Virus Vector Transduction						
Achromatopsia	1/2	AAV2tYF	*CNGB3*	AGTC	Open
	1/2	AAV2/8	*CNGB3*	MeiraGTx	Completed
	1/2	AAV2tYF	*CNGA3*	AGTC	Open
	1/2	AAV2/8	*CNGA3*	MeiraGTx	Open
	1/2	AAV8	*CNGA3*	Tuebingen	Completed
XL RS	1/2	AAV2tYF	*RS1*	AGTC	Closed
	1/2	AAV8	*RS1*	NIH	Open
XL RP	1/2 → 2	AAV2tYF	*RPGR*	AGTC	Open
	2 → 3	AAV2/8	*RPGR*	Biogen	Open
	1/2	AAV2/5	*RPGR*	MeiraGTx	Open
	1/2	?	*RPGR*	4D	Open
RP	1/2	AAV2/5	*PDE6B*	Horama S.A.	Open
Choroideremia	3	AAV2	*REP1*	Biogen	Open
	1/2	AAV2	*REP1*	Spark	Open
	2	AAV2	*REP1*	Tuebingen	Open
	2	AAV2	*REP1*	U of Oxford	Open
	2	AAV2	*REP1*	Bascom	Completed
	1/2	AAV2	*REP1*	U of Alberta	Completed
	1	AAV2	*REP1*	4D	Open
LCA2/RP	Approved	AAV2	*RPE65*	Spark	Treating
LCA1	1/2	AAV5	*GUCY2D*	Atsena	Open

Lentivirus Vector Transduction					
Stargardt	1/2	EIAV	*ABCA4*	Sanofi	Closed
Usher 1B	1/2	EIAV	*MYO7A*	Sanofi	Closed
Antisense Oligonucleotide					
RP/Usher 2	1/2	*USH2A* (exon 13)		ProQR	Enrolling
RP	1/2	*RHO* (P23H)		ProQR	Enrolling
LCA	1/2	*CEP290* (p.Cys998X)		ProQR	Enrolling
Gene Editing/CRISPR					
LCA	1/2	*CEP290* (p.Cys998X)		Editas	Enrolling
Optogenetics					
RP	2	AAV2-MCO		Nanoscope	Enrolling
RP	1/2	AAV2-7m8		GenSight	Enrolling

Courtesy of Paul Yang, AAO 2020

The open-label dose-ranging safety and efficacy trial is recruiting at least 12 adults to be assigned to one of four consecutive cohorts. The primary endpoint is the incidence of adverse events, with 4-year follow-up after the initial 12-month trial. Secondary endpoints include improvements in visual fields, visual function, and quality of life.

An optogenetics trial that uses the AAV2 vector to deliver multi-characteristic opsin (MCO)—light sensitive molecules—to retinal cells is showing promise as a mutation-independent gene therapy for advanced RP. In the phase 1/2a study, 11 patients received a single intravitreal injection of **MCO-010 (Nanoscope Therapeutics)**.[7,8] At 12 months, six of seven (86%) high-dose patients gained > 0.3 logMAR (15 letters). Data also showed that shape discrimination accuracy improved to > 90% in all patients compared with baseline, and performance in mobility testing improved by a 50% reduction in the time it took for patients to touch a lighted panel. In June, Nanoscope announced that the FDA had approved the company's investigational new drug application for a phase 2b optogenetics trial.[9]

Researchers in the phase 1/2 study of **GenSight Biologics' GS030** gene therapy program reported a case detailing one patient with a 40-year history of RP who experienced partial recovery of visual function after treatment.[10,11]

GS030 combines delivery of a gene therapy product encoding a photoactivatable channelrhodopsin protein with use of light-stimulating goggles. The patient received the lowest dose of the gene therapy, followed by training with the device 4.5 months later. After 7 months of training, the patient reported signs of visual improvement, with the ability to perceive, locate, count, and touch objects when using the goggles. In addition, electroencephalography suggested that performing the visual perception tests caused neurophysiologic activity in the visual cortex.[11]

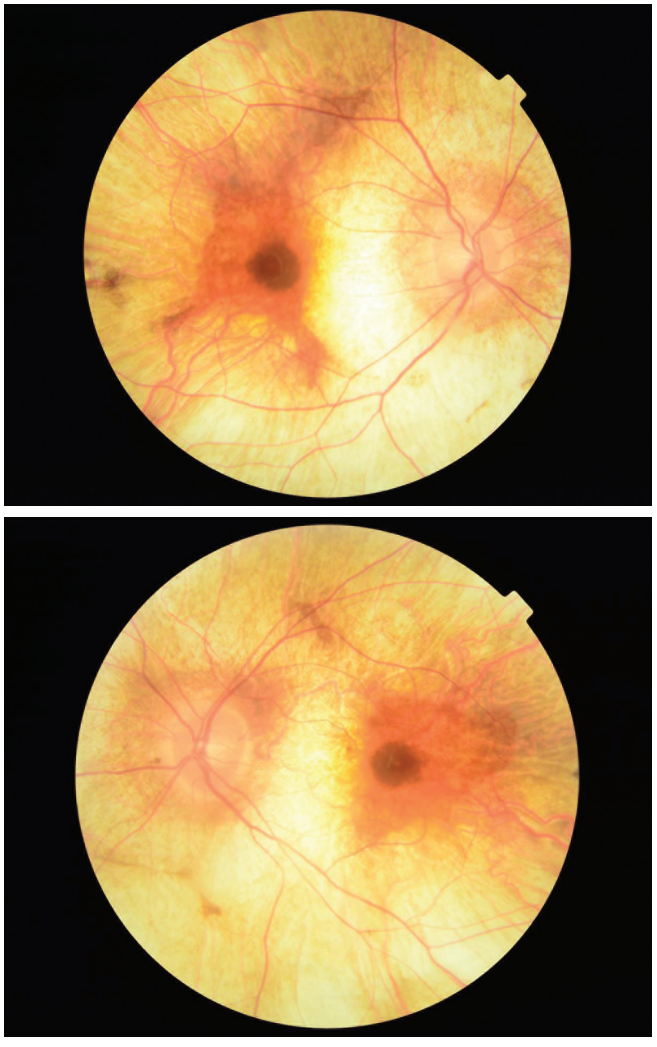


Figure. Retina specialists should follow the gene therapy trials carefully, as they may one day provide a therapy option for patients with IRDs, such as this one with choroideremia.

OTHER TRIALS IN THE PIPELINE

Several therapeutics in development are using means other than AAV vectors to achieve delivery.

Sepofarsen (QR-110, ProQR) is an antisense oligonucleotide designed to address the underlying cause of LCA 10 due to the p.Cys998X mutation in the *CEP290* gene. The phase 1b/2 study found that the treatment was well tolerated, and patients demonstrated improvement in BCVA, full field stimulus threshold test, and mobility. However, treatment was associated with cataract development.[1] The phase 2/3 study completed enrollment of 36 patients with random assignment to one of two dosing groups or a control arm.[2]

A phase 1/2 clinical trial of the antisense oligonucleotide **QR-421a (ProQR)** in adults with Usher syndrome and nonsyndromic RP due to *USH2A* exon 13 mutations demonstrated benefits in visual acuity, visual fields, and OCT imaging. The company is planning pivotal phase 2/3 trials.[3]

The antisense oligonucleotide **QR-1123 (ProQR)** is in a phase 1/2 clinical trial for adult patients with RP due to the P23H mutation in the *RHO* gene. The trial is enrolling approximately 35 patients and will include up to eight single-dose and repeat-dose cohorts. Patients will be followed for 12 months to assess safety, tolerability, and efficacy.[4]

AGN-151587 (EDIT-101, Allergan/Editas) is the first in vivo CRISPR therapy, according to the developers; it is being evaluated in a phase 1/2 trial including approximately 18 pediatric and adult patients with LCA 10. The actively recruiting trial will assign patients into one of five dosing cohorts. Primary outcomes at 1 year include frequency of treatment-related adverse events, procedure-related adverse events, and incidence of dose-limiting toxicities.[5]

1. Russell SR, Drack AV, Cideciyan AV, et al. Results of a phase 1b/2 trial of intravitreal (IVT) sepofarsen (QR-110) antisense oligonucleotide in Leber congenital amaurosis 10 (LCA10) due to p.Cys998X mutation in the CEP290 gene. *Invest Ophthalmol Vis Sci*. 2020;61:866.
2. A study to evaluate efficacy, safety, tolerability and exposure after a repeat-dose of sepofarsen (QR-110) in LCA10 (Illuminate). Accessed June 2, 2021. clinicaltrials.gov/ct2/show/NCT03913143
3. ProQR announces positive results from clinical trial of QR-421a in Usher syndrome and plans to start pivotal trials [press release]. ProQR. March 24, 2021. Accessed June 2, 2021. www.proqr.com/press-releases/proqr-announces-positive-results-from-clinical-trial-of-qr-421a-in-usher-syndrome-and-plans-to-start-pivotal-trials
4. A study to evaluate the safety and tolerability of QR-1123 in subjects with autosomal dominant retinitis pigmentosa due to the P23H mutation in the RHO gene (Aurora). Accessed June 2, 2021. clinicaltrials.gov/ct2/show/NCT04123626
5. Single ascending dose study in participants with LCA10. Accessed June 2, 2021. clinicaltrials.gov/ct2/show/NCT03872479

X-Linked Retinoschisis

A phase 1/2 study at the US National Eye Institute is evaluating three increasing dose levels of an **AAV-RS1 vector** for the treatment of X-linked retinoschisis. Up to 24 adult patients with VA of 20/63 or worse in one eye will be included. Ocular events reported to date include dose-related inflammation that resolved with corticosteroids. Systemic antibodies against AAV8 increased in a dose-related fashion, but no antibodies against retinoschisin 1 were observed.[12]

Choroideremia

An ongoing phase 1/2 trial in patients with choroideremia is using an AAV2 vector, **AAV2-hCHM (Spark Therapeutics)**.[13] In preliminary 6-month safety data, visual acuity returned to baseline in all but one patient, who gradually returned to within 20 ETDRS letters of baseline by month 6.[14] Foveal thinning was observed in this patient. Mean sensitivity, as assessed by light-adapted perimetry, remained unchanged in both treated and control eyes.

A phase 1 dose-escalation study of **4D-110 (4D Molecular Therapeutics)** gene therapy is evaluating the safety, tolerability, and preliminary efficacy of a single intravitreal injection at two dose levels in patients with choroideremia.[15] 4D-110 is an AAV capsid variant carrying a transgene encoding a codon-optimized human *CHM* gene.

Achromatopsia

Two phase 1/2 open-label multicenter dose-escalation trials are investigating gene therapies for achromatopsia: One trial is evaluating **AAV2/8-hG1.7p.coCNGA3 (AAV-CNGA3, MeiraGTx/Janssen)** in patients with *CNGA3*-associated achromatopsia, and another is evaluating **AAV2/8-hG1.7p.coCNGB3 (AAV-CNGB3, MeiraGTx/Janssen)** in patients with *CNGB3*-associated achromatopsia.[16,17] The primary outcome measure for each of the trials is incidence of treatment-related adverse events at 6 months. Secondary outcome measures include assessments of improvement of visual function, retinal function, and quality of life.

AGTC is also enrolling patients in two nonrandomized open-label phase 1/2 studies evaluating the safety and efficacy of its two gene therapy candidates, **rAAV2tYF-PR1.7-hCNGA3 (AGTC-402)** for patients with *CNGA3*-associated achromatopsia and **rAAV2tYF-PR1.7-hCNGB3 (AGTC-401)** for patients with *CNGB3*-associated achromatopsia.[18,19] Participants were sequentially assigned to one of four dose groups in both studies.

The company recently reported interim 12-month safety and efficacy findings, and both therapies were well tolerated across all dose ranges. Most adverse events were mild to moderate, and no serious adverse events were treatment-related. Four of the 24 treated participants had a five-letter improvement in BCVA at month 12. Five participants had a 1-log^{10} lux or more improvement in light sensitivity threshold.[20] AGTC intends to complete enrollment and has amended the study protocol to allow enrollment of patients as young as age 4 years.[20,21]

Leber Congenital Amaurosis

A phase 1/2 study sponsored by Atsena Therapeutics is investigating the safety and tolerability of ascending doses of **AAV5-hGRK1-GUCY2D**, administered via

subretinal injection, in patients with *GUCY2D*-associated Leber congenital amaurosis. The trial is recruiting approximately 15 patients who are at least 6 years old and will assign them to one of five dosing groups. The primary endpoint is the number of patients with adverse events; secondary endpoints include change in BCVA and change in retinal sensitivity as measured by full-field stimulus testing.[22]

TRIALS IN THE WINGS

The phase 2/3 XIRIUS study of **cotoretigene toliparvovec (BIIB112, Biogen)** for *RPGR*-associated XLRP failed to hit its primary endpoint of a statistically significant improvement in the percentage of treated eyes with a ≥ 7 dB improvement from baseline at ≥ 5 of 16 central loci.[23] Nonetheless, the company observed positive trends across some secondary endpoints, including low luminance visual acuity.

A phase 1/2 study sponsored by the University of Oxford evaluated a single subretinal injection of **AAV2-REP1** in patients with choroideremia and found that two patients with advanced choroideremia and low baseline BCVA gained 21 letters and 11 letters.[24] The early improvement in two of the six patients was sustained at 3.5 years, despite progressive degeneration in the control eyes.[25] A phase 2 open-label study remains open but not recruiting.[26]

These data prompted Biogen's phase 3 study of **timrepigene emparvovec (BIIB111/AAV2-REP1)**, which randomly assigned 170 adult patients with choroideremia to one of three dosing groups. The study's primary endpoint is the percentage of patients with a ≥ 15-letter improvement in BCVA from baseline at 12 months.[27] In June, the company announced that this primary efficacy endpoint was not met.[28]

A phase 1/2 study evaluated the delivery of **AAV2tYF-CB-hRS1 (AGTC)** in patients with X-linked retinoschisis. Results supported the general safety and tolerability of the gene delivery platform but did not demonstrate signs of clinical activity at 6 months.[29]

Sanofi-sponsored lentivirus-based clinical trials for Stargardt and Usher syndrome type 1B were both prematurely terminated.[30,31] According to clinicaltrials.gov, the decision was not due to safety concerns, but rather because Sanofi decided to stop development of the product.

FINAL THOUGHTS

Much work remains to be done, but IRD research has advanced monumentally in the past 10 years. With the FDA approval of voretigene, the field of ocular gene therapy has exploded, and the number of trials provides hope for IRD patients who are waiting for a potential treatment.

With standard augmentation gene therapy, novel optogenetic therapies, and other advances such as antisense oligonucleotide therapy, we must remain up to date on recent research to provide the best possible care for our patients. ■

1. Gene therapy for X-linked retinitis pigmentosa (XLRP) retinitis pigmentosa GTPase regulator (RPGR). Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT03252847
2. MeiraGTx announces nine-month data from phase 1/2 trial of AAV-RPGR demonstrating significant and sustained vision improvement in X-linked retinitis pigmentosa (XLRP) [press release]. MeiraGTx. October 3, 2020. investors.meiragtx.com/news-releases/news-release-details/meiragtx-announces-nine-month-data-phase-12-trial-aav-rpgr. Accessed May 26, 2021.
3. Safety and efficacy of rAAV2tYF-GRK1-RPGR in subjects with X-linked retinitis pigmentosa caused by RPGR mutations. Accessed May 26, 2021. clinicaltrials.gov/ct2/show/NCT03316560
4. AGTC reports additional positive data from its phase 1/2 clinical trial in patients with X-linked retinitis pigmentosa [press release]. AGTC. November 11, 2020. Accessed May 26, 2021. agtc.com/agtc-reports-additional-positive-data-from-its-phase-1-2-clinical-trial-in-patients-with-x-linked-retinitis-pigmentosa
5. 4D-125 in patients with X-Linked retinitis pigmentosa (XLRP). Accessed June 24, 2021. clinicaltrials.gov/ct2/show/NCT04517149
6. Safety and efficacy study in patients with retinitis pigmentosa due to mutations in PDE6B gene. Accessed May 27, 2021. clinicaltrials.gov/ct2/show/NCT03328130
7. Nanoscope Therapeutics. Nanoscope's optogenetic gene therapy restores clinically meaningful vision in 11 patients blinded by retinitis pigmentosa [press release]. June 3, 2021. Accessed June 7, 2021. nanostherapeutics.com/2021/06/03/nanoscopes-optogenetic-gene-therapy-restores-clinically-meaningful-vision
8. Dose-escalation study to evaluate the safety and tolerability of intravitreal vMCO-1 in patients with advanced retinitis pigmentosa. Accessed June 16, 2021. clinicaltrials.gov/ct2/show/NCT04919473
9. Nanoscope Therapeutics. Nanoscope Therapeutics announces FDA approval of IND for phase 2b clinical trial of optogenetic gene monotherapy to restore vision in patients with retinitis pigmentosa [press release]. June 23, 2021. Accessed June 23, 2021. prnewswire.com/news-releases/nanoscope-therapeutics-announces-fda-approval-of-ind-for-phase-2b-clinical-trial-of-optogenetic-gene-monotherapy-to-restore-vision-in-patients-with-retinitis-pigmentosa-301318044.html
10. Dose-escalation study to evaluate the safety and tolerability of GS030 in subjects with retinitis pigmentosa (PIONEER). Accessed June 16, 2021. clinicaltrials.gov/ct2/show/NCT03326336
11. Sahel JA, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. Published online May 1, 2021. *Nat Med*.
12. Cukras C, Wiley HE, Jeffrey BG, et al. Retinal AAV8-RS1 gene therapy for X-linked retinoschisis: Initial findings from a phase I/IIa trial by intravitreal delivery. *Mol Ther*. 2018;26(9):2282-2294.
13. Safety and dose escalation study of AAV2-hCHM in subjects with CHM (choroideremia) gene mutations. Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT02341807.
14. Aleman TSSL, Han GK, Pearson DJ. AAV2-hCHM subretinal delivery to the macula in choroideremia: preliminary six month safety results of an ongoing phase I/II gene therapy trial. *Invest Ophthalmol Vis Sci*. 2017;58:4485.
15. Dose escalation study of intravitreal 4D-110 in patients with choroideremia. Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT04483440
16. Gene therapy for achromatopsia (CNGA3) (CNGA3). Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT03758404
17. Gene therapy for achromatopsia (CNGB3) (CNGB3). Accessed May 26, 2021. clinicaltrials.gov/ct2/show/NCT03001310
18. Safety and efficacy trial of AAV gene therapy in patients with CNGA3 achromatopsia. Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT02935517
19. Safety and efficacy trial of AAV gene therapy in patients with CNGB3 achromatopsia. Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT02599922
20. Pennesi ME, Yang P, Lauer A, et al. Twelve-month findings from two phase 1/2 clinical studies of subretinal gene therapy drugs for achromatopsia. Paper presented at: ARVO 2021; May 6, 2021.
21. AGTC announces financial results and business update for the quarter ended September 30, 2020 [press release]. AGTC. November 16, 2020. Accessed May 26, 2021. ir.agtc.com/news-releases/news-release-details/agtc-announces-financial-results-and-business-update-quarter-11
22. Study of subretinally injected SAR439483 administered in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D. Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT03920007
23. Biogen announces topline results from phase 2/3 gene therapy study for XLRP [press release]. Biogen. May 14, 2021. Accessed June 7, 2021. investors.biogen.com/news-releases/news-release-details/biogen-announces-topline-results-phase-23-gene-therapy-study
24. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: Initial findings from a phase 1/2 clinical trial. *Lancet*. 2014;383(9923):1129-1137.
25. Edwards TL, Jolly JK, Groppe M, et al. Visual acuity after retinal gene therapy for choroideremia. *N Engl J Med*. 2016;374:1996-1998.
26. REP1 gene replacement therapy for choroideremia (REGENERATE). Accessed June 16, 2021. clinicaltrials.gov/ct2/show/NCT02407678
27. Efficacy and safety of BIIB111 for the treatment of choroideremia (STAR). Accessed June 7, 2021. clinicaltrials.gov/ct2/show/NCT03496012
28. Biogen announces topline results from phase 3 gene therapy study in choroideremia [press release]. Biogen. June 14, 2021. Accessed June 16, 2021. investors.biogen.com/news-releases/news-release-details/biogen-announces-topline-results-phase-3-gene-therapy-study
29. Safety and efficacy of rAAV-hRS1 in patients with X-linked retinoschisis (XLRS). Accessed June 7, 2021. clinicaltrials.gov/ct2/show/results/NCT02416622.
30. Phase I/IIA study of SAR422459 in participants with Stargardt's macular degeneration. Accessed June 16, 2021. clinicaltrials.gov/ct2/show/NCT01367444
31. Study of SAR421869 in participants with retinitis pigmentosa associated with Usher syndrome type 1B. Accessed June 16, 2021. clinicaltrials.gov/ct2/show/results/NCT01505062

CHRISTINE KAY, MD

- Vitreoretinal Surgeon, Director of Electrophysiology and Retinal Genetics, Vitreoretinal Associates, Gainesville, Florida
- Affiliate Assistant Professor of Ophthalmology, University of South Florida, Tampa, Florida
- christinenkay@gmail.com
- Financial disclosure: Consultant (AGTC, Spark, Atsena, 4D); Clinical Trial Funding (AGTC, Biogen, MeiraGTx, ProQR)

Tips and Tricks for Evaluating Children for Inherited Retinal Degenerations

Novel therapeutics and those in the pipeline are changing how we care for patients with IRDs. Here's what you need to know.

BY DAVID XU, MD; MICHAEL N. COHEN, MD; MICHAEL A. KLUFAS, MD; AND JOSE S. PULIDO, MD, MS, MBA, MPH

A young child referred to a retina specialist raises many concerns. Have they seen a pediatric ophthalmologist, or is this just a failed vision screening with type A parents? How do I examine an uncooperative child in the clinic? How much time will it take to explain the diagnosis and plan to the parents?

In this article, clinically useful tips and expert opinion provide a framework to make the clinical approach to young patients with inherited retinal diseases (IRDs) easier.

DIAGNOSTIC CHALLENGES

Historically, IRDs have been classified according to natural history: stationary or progressive, mode of inheritance (autosomal dominant or recessive, X-linked, or mitochondrial), and principal site of dysfunction (retinal pigment epithelium, rod or cone photoreceptors, or inner retina). This approach relies on careful and extensive history, clinical examination, multimodal imaging, and, often, electrophysiologic testing.

Even with this information, the molecular pathophysiology in this clinically and genetically heterogeneous group of dystrophies may not be apparent. In addition, young patients may be more difficult to examine, may have more subtle visual complaints, and may have associated disorders.

Advances in molecular genetics have allowed more precise classification based on genetic mutations and the associated pathophysiologic defects that lead to retinal dysfunction (Figure).

Genetic testing has also undergone a revolution, and multiplex gene sequencing has enabled screening for a wide panel of genes associated with retinal dystrophies.

The potential benefits of genetic testing are obvious: It can establish a molecular diagnosis, potentially avoid electrophysiologic testing, and establish candidacy for gene therapy. However, panel testing can also uncover "variants of uncertain significance," the majority of which represent normal genetic variations rather than a causative mutation. Such a finding can create uncertainty and frustration for the physician and family.

AT A GLANCE

- Evaluating children for inherited retinal diseases (IRDs) involves clinical examination and fundoscopy, genetic testing, and electrophysiologic testing.
- Syndromic conditions associated with early-onset IRDs can present with various systemic manifestations; the key is to home in on patterns of disease to help narrow the differential diagnosis.
- A causative mutation can be identified in 60% to 80% of patients with IRDs.

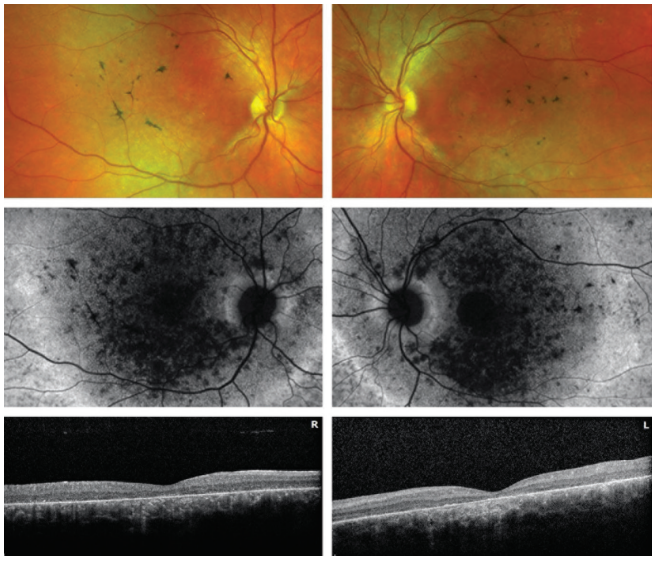


Figure. This 19-year-old woman presented with long-standing vision loss with a VA of counting fingers OD and 20/400 OS. Fundus examination (top) showed macular atrophy and pigment hyperplasia, fluorescein angiography (middle) demonstrated hypoautofluorescence with peripapillary sparing, and OCT (bottom) showed bilateral widespread ellipsoid zone and retinal pigment epithelium attenuation consistent with Stargardt disease. Genetic testing of the *ABCA4* gene revealed a heterozygous nonsense mutation *Q1029X* and *F418S* variant of unknown significance.

THE PEDIATRIC EVALUATION

There are three key elements to consider in the evaluation of IRDs in children.

1. Clinical examination and fundoscopy; a challenge here is that some IRDs, such as congenital stationary night blindness (CSNB), retinitis pigmentosa (RP) sine pigmento, and others, present with minimal to no retinal changes on examination;
2. Genetic testing; and
3. Electrophysiologic testing (full-field and/or multifocal electroretinogram [ERG] and electrooculogram).

The first objective is to establish a diagnosis and confirm that an IRD is responsible for the vision loss. The most common visual complaints, as reported by parents, include nystagmus, vision loss, and photophobia.[1] If disease onset is earlier than 6 months, nystagmus is often the earliest complaint.

A thorough medical and ocular history is important for all patients, including best available visual acuity, refraction, and careful anterior segment examination. Teller acuity or other pediatric vision tests can be performed in preverbal children.

Clinicians should also evaluate for systemic abnormalities such as hearing loss, renal dysfunction, extra digits, and neurologic dysfunction. In uncooperative children, examination under anesthesia may be necessary for a complete fundus examination. Fundus photography, fluorescein angiography, fundus autofluorescence, and full-field ERG can help narrow the differential diagnosis. The benefits of a sedated examination should be weighed against the risks (such as depression of ERG waveforms).

Visual field testing can help monitor progression of a rod-cone dystrophy or make a determination of legal blindness or disability. Examination of other family members and documentation of a complete pedigree may provide information on the mode of transmission and illuminate implications for siblings and other family members.

SYSTEMIC ASSOCIATIONS

Syndromic conditions associated with early-onset retinal degeneration can present with a variety of manifestations. The key is to home in on patterns of disease to help narrow the diagnosis and refer patients for appropriate screenings. Following is a selected list of conditions to look out for.[2]

Retinal ciliopathies—Usher, Bardet-Biedl, Senior Loken, Joubert, and other syndromes—arise from genetic defects affecting photoreceptors and other cellular cilia, leading to an RP-like phenotype. Usher syndrome, caused by mutations in at least 11 known genes, leads to progressive retinal degeneration and hearing loss. Bardet-Biedl syndrome produces a constellation of findings including cone-rod dystrophy, polydactyly, obesity, and hypogonadism. Senior Loken is a rare autosomal recessive disorder characterized by an RP or Leber congenital amaurosis (LCA) phenotype associated with juvenile nephronophthisis, causing cystic degeneration of the kidneys. Joubert syndrome can be associated with hypotonia, ataxia, and a characteristic "molar tooth sign" on MRI of the brain. Although the manifestations of ciliopathies are quite pleomorphic, it is important to identify patterns of disease and initiate the appropriate workup.[2]

Neuronal ceroid lipofuscinoses, such as juvenile CLN3, are progressive neurodegenerative disorders caused by abnormal accumulation of lipofuscin and lipid deposits. Retinal degeneration can predate the other manifestations. Unfortunately, patients develop neurologic decline and loss of motor coordination and die in their teens or 20s.[2]

Refsum disease is a peroxisomal storage disorder that presents with ichthyosis, ataxia, and RP. Dietary restriction of phytanic acid and plasmapheresis are standard treatments.[2]

Ocular mitochondrial disorders can affect the optic nerve or retinal ganglion cells or can lead to a pigmentary retinopathy. Those with retinal manifestations include chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, and others. These can be associated with ptosis, ophthalmoplegia, cardiac myopathy, and seizure.[2]

GENETIC TESTING BASICS

Testing can play an important role in achieving the correct diagnosis and determining eligibility for investigational gene therapies. A causative mutation can be identified in 60% to 80% of patients with IRDs, and most often a saliva sample (2 mL) is sufficient for initial panel testing.[3] Several

commercial retinal dystrophy panels are available in the United States, and CLIA-approved gene sequencing laboratories can also perform testing.

However, hereditary dystrophies are quite heterogeneous; more than 260 genetic loci have been implicated in retinal dystrophies, and different mutations of a single gene can be responsible for different phenotypes. For example, RP can be caused by mutations in one of 84 different genes, and cone-rod dystrophy can be caused by mutations in one of 33 genes.

Next-generation sequencing methods have enabled the creation of IRD panels that can screen a large number of candidate genes, and approximately two-thirds of patients overall and up to 85% of children with IRDs can receive a genetic diagnosis.[4] Single gene analysis with traditional Sanger sequencing is more appropriate for monogenic diseases or when only a specific gene or set of genes is believed to be causative. The AAO's Task Force on Genetic Testing recommends that clinicians order the most specific test or tests available based on each patient's clinical findings.[5]

The potential outcome of genetic testing should be considered prior to ordering the panel. For example, the results could either confirm the suspected diagnosis, be inconclusive, or be negative for all tested genes. Referral to a geneticist or genetic counselor can be helpful in the child's workup and treatment, and also for family planning purposes.

Segregation analysis with a familial pedigree can help to clarify the inheritance pattern and establish when more than one copy of a gene is in cis or trans configuration. This can have important consequences for families considering additional children and for their children's reproductive future.

TREATMENT ADVANCES

Management of IRDs has traditionally been limited to genetic counseling, low-vision referral, management of systemic associations, and educational or occupational therapy. But the era of gene-based ocular therapy for IRDs began with the FDA approval of voretigene neparvovec (Luxturna, Spark) to treat *RPE65*-associated LCA. Numerous clinical trials are evaluating therapeutic candidates for X-linked RP, Stargardt disease, achromatopsia, choroideremia, X-linked retinoschisis, and others. With increased genetic testing and targeted therapies, the therapeutic armamentarium will hopefully evolve.

TAKEAWAYS

IRDs are a heterogeneous group of degenerative disorders that negatively impact patients' autotomy and vision. Achieving a diagnosis can be challenging, especially in young patients, but it is key to successful management. Careful clinical examination and history-taking, genetic testing, and ERG evaluation all play important roles. Diagnosis now opens the door to gene therapy for those with *RPE65*-associated LCA and for clinical trial elibility for many others. Continued advances in genetic testing and better understanding of pathogenic variants will continue to provide hope for patients with these orphan diseases. ■

RAPID-FIRE CASES

A 2-year-old girl with infantile nystagmus was referred for possible achromatopsia due to intense photophobia since birth. Low hyperopia was present on cycloplegic refraction. Given her age, an ERG would have to be obtained under anesthesia. Instead, genetic testing was ordered, revealing a negative result for achromatopsia but a positive LCA panel for *CEP290*, obviating the need for ERG.

A 3-year-old boy was referred for decreased vision and was found to have -6.00 D myopia. The fundus examination was unremarkable, making it difficult to distinguish his condition from other retinal degenerations. However, myopia is more often associated with X-linked and autosomal recessive variants of CSNB rather than LCA. Visual fields should remain stable in CSNB, unlike in RP. A paradoxical pupillary response (initial constriction of pupil when ambient light is dimmed) may be seen with CSNB.

1. Suppiej A, Marino S, Reffo ME, et al. Early onset retinal dystrophies: clinical clues to diagnosis for pediatricians. *Ital J Pediatr*. 2019;45(1):168.
2. Fasiuddin A. Inherited retinal degenerations. *International Ophthalmology Clinics*. 2010;50(4):45-56.
3. Tsang SH, Sharma T. Genetic testing for inherited retinal dystrophy: basic understanding. *Adv Exp Med Biol*. 2018;1085:261-268.
4. Duncan JL, Pierce EA, Laster AM, et al. Inherited retinal degenerations: current landscape and knowledge gaps. *Transl Vis Sci Technol*. 2018;7(4):6.
5. American Academy of Ophthalmology. Recommendations for genetic testing of inherited eye diseases - 2014. Accessed June 3, 2021. www.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d

MICHAEL N. COHEN, MD
- Vitreoretinal Surgeon, Wills Eye Hospital, Mid Atlantic Retina, Philadelphia
- Assistant Professor of Ophthalmology, Thomas Jefferson University, Philadelphia
- Financial disclosure: Consultant (Allergan, Keeler)

MICHAEL A. KLUFAS, MD
- Vitreoretinal Surgeon, Wills Eye Hospital, Mid Atlantic Retina, Philadelphia
- Assistant Professor of Ophthalmology, Thomas Jefferson University, Philadelphia
- Retina Chief, Eyetube.net
- mklufas@midatlanticretina.com
- Financial disclosure: Consultant (Allergan, Novartis, Genentech); Speaker (Genentech, Regeneron)

JOSE S. PULIDO, MD, MS, MBA, MPH
- Larry Donoso Chair of Translational Ophthalmology, Wills Eye Hospital, Philadelphia
- Professor Emeritus, Departments of Ophthalmology and Molecular Medicine, Mayo Clinic, Rochester, Minnesota
- Financial disclosure: iPSC-RPE Cell Delivery Patents (Mayo Clinic)

DAVID XU, MD
- Vitreoretinal Surgeon, Wills Eye Hospital, Mid Atlantic Retina, Thomas Jefferson University Hospitals, Philadelphia
- davidxu64@gmail.com
- Financial disclosure: None

eyetube

NEW ON THE RETINA CHANNEL

Editorial Features group together multiple types of content centered around one particular topic. These editorially independent features could include supplements, podcasts, video series, and more.
Find this content and more at: eyetube.net/retina

Arshad M. Khanani, MD, MA, moderates a roundtable discussion with Christopher G. Fuller, MD; Nikolas J.S. London, MD, FACS; and Christina Y. Weng, MD, MBA, that addresses the modern challenges of wet AMD management. Dr. Khanani and the roundtable participants address questions of real-world safety, summarize late-phase and early-phase clinical trial data, and share cases of challenging patients.

Although vitreous opacities or floaters symptoms are minimal in most patients, they can cause significant impairment in vision-related quality of life in some patients. This panel discussion provides an overview of symptomatic vitreous opacities and their treatment options, discusses best practices in patient identification for surgical treatment, reviews surgical pearls for vitrectomies and the role of laser treatment, and provides clarity around the treatment approach to optimize outcomes.

Carl Regillo, MD, moderates a roundtable discussion with Caroline Baumal, MD; Usha Chakravarthy, MD, PhD, CBE; and Rishi Singh, MD; that addresses the modern challenges of treatment adherence in patients with neovascular AMD. Dr. Regillo and the roundtable participants address questions of real-world safety, summarize late-phase and early-phase clinical trial data, and share cases of challenging patients.

Localized Steroid Therapy for Chronic Noninfectious Posterior Uveitis

A review of recent literature and an illustrative case highlight the pros and cons of this treatment option.

BY SUMIT SHARMA, MD

Patients with chronic noninfectious uveitis of the posterior segment (NIU-PS) have a number of therapeutic options, including systemic therapy, short-duration local antiinflammatory therapy, and long-duration local antiinflammatory therapy. Innovations in the latter option have the potential to reduce patients' treatment burden while also offering relief from NIU-PS.

A review of recent literature illustrates why long-duration steroid therapy for NIU-PS can be effective, efficient, and economical. This article focuses on data related to the fluocinolone acetonide intravitreal implants 0.18 mg (Yutiq, EyePoint Pharmaceuticals) and 0.59 mg (Retisert, Bausch + Lomb). The case that follows demonstrates the effect local therapy can have on patients with NIU-PS.

THREE-YEAR RESULTS

Last year Jaffe et al published 3-year results of a phase 3 trial assessing the safety and efficacy of the fluocinolone acetonide intravitreal implant 0.18 mg for the treatment of NIU-PS.[1]

Patients were randomly assigned 2:1 to receive treatment with the implant (n = 87) or sham injection plus standard of care (n = 42). Outcomes were evaluated at 36 months.

The researchers found that patients in the treatment group experienced significantly fewer cumulative uveitis recurrences compared with those in the sham group (66% vs 98%, $P < .001$), and also had a longer median time to first recurrence (657 days vs 71 days, $P < .001$). Patients in the sham group experienced a mean 5.3 recurrences during the study period

AT A GLANCE

- Noninfectious posterior uveitis patients treated with the fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq, EyePoint Pharmaceuticals) experienced significantly lower disease recurrence compared with patients who received the sham.
- Although 7-year data from the MUST study suggested that systemic steroid therapy resulted in superior visual gains from baseline compared with local steroid therapy, some authors have argued that this conclusion may be flawed.
- Long-term sustained-release local therapy may result in positive outcomes for patients with noninfectious posterior uveitis.

HUNGRY FOR MORE UVEITIS LITERATURE?

Here are a few bite-sized summaries.

Fellow-Eye Data at 3 Years

Patients with bilateral NIU-PS in a phase 3 study evaluating the fluocinolone acetonide intravitreal implant 0.18 mg received therapy in the eye with worse disease, leaving the other eye as a natural history study of disease progression. At 3 years, untreated fellow eyes had higher rates of uveitis recurrence and local steroid injections. Rates of IOP elevations and use of IOP-lowering medication were similar between the implant-treated and fellow eyes.[1]

Cost-Effectiveness of Localized Steroid Therapy

The fluocinolone acetonide intravitreal insert 0.19 mg (Iluvien, Alimera Sciences), FDA-approved to treat diabetic macular edema, is approved to treat NIU-PS in the United Kingdom.[2] The UK National Institute for Health and Care Excellence evaluated the cost-effectiveness of the 0.19-mg implant for the treatment of recurrent NIU-PS and found that the treatment was a cost-effective use of National Health Service resources.[3]

1. Sharma S. Course of non-infectious uveitis affecting the posterior segment: fellow-eye data from a 3-year study of the fluocinolone acetonide intravitreal insert. *Invest Ophthalmol Vis Sci*. 2020;61(7):5364.
2. Alimera Sciences. Alimera Sciences announces approval received in the mutual recognition procedure for new indication for Iluvien in Europe [press release]. March 25, 2019. Accessed June 9, 2021. investors.alimerasciences.com/prviewer/release_only/id/3700779
3. Pouwels XG, Petersohn S, Carrera VH, et al. Fluocinolone acetonide intravitreal implant for treating recurrent non-infectious uveitis: an evidence review group perspective of a NICE single technology appraisal. *PharmacoEconomics*. 2020;38(5):431-441.

compared with 1.7 recurrences in the treatment group ($P < .001$). Nearly all participants in the sham group (98%) required adjunctive treatment compared with 58% of treated patients.[1]

Although IOP at month 36 was similar in both study arms, approximately 6% of eyes in the treatment group required IOP-lowering surgery compared with almost 12% in the sham group. Cataract surgery was required in approximately 74% of eyes in the treatment arm compared with almost 24% of eyes in the sham arm. The study authors concluded that the side effect profile of treatment with the implant was acceptable compared with sham-treated eyes.[1]

SEVEN-YEAR DATA DEBATE

In the Multicenter Uveitis Steroid Treatment (MUST) trial, first published in 2011, patients with noninfectious intermediate, posterior, or panuveitis were randomly assigned to receive systemic steroid therapy or the fluocinolone acetonide intravitreal implant 0.59 mg.[2] Researchers determined that both therapy options resulted in similar improvements in visual acuity at 24 months. Although patients in the implant group had higher rates of cataract formation, elevated IOP, and glaucoma, they also experienced greater improvement from baseline in vision-related quality of life and lower rates of residual active uveitis.

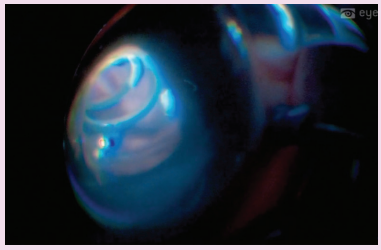
After 7 years of follow-up in MUST, patients in the treatment arm lost 5.9 letters from baseline, whereas those who underwent systemic therapy gained 1.2 letters.[3] The difference was considered clinically significant.

Publication of these 7-year data resulted in some disagreement among uveitis specialists, and a 2019 editorial by Albini et al outlined concerns about the study's structure and conclusions.[4] For example, the authors argued, because the MUST study was not designed to evaluate outcomes at 7 years, conclusions about efficacy at 7 years cannot be drawn. The authors also noted that 85% of patients randomly assigned to receive the implant had it implanted within 3 years, and only 27% of those patients received an implant in the 3 years preceding the 7-year timepoint. By contrast, 64% of patients in the systemic therapy arm received some form of treatment in the 6 months before the 7-year timepoint. Given that the implant releases its drug for an average 3 years,[5] Albini et al noted therefore that most patients in the local therapy arm were not being dosed with fluocinolone acetonide at the 7-year endpoint, whereas most patients in the systemic arm were receiving treatment late in the study period. In addition, some patients in the systemic arm had previously undergone treatment with the fluocinolone acetonide intravitreal implant 0.59 mg.

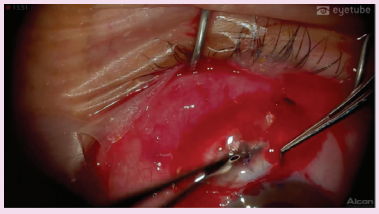
Albini et al concluded that the 7-year data, although perhaps useful for generating hypotheses, do not necessarily reverse the primary finding of the original 2-year study. Clinicians treating uveitis, they suggested, should still consider a sustained-release fluocinolone implant as an option for certain patients.[4]

LEARN MORE ABOUT RETISERT

In these two surgical videos, Thomas Aaberg Jr, MD, and Chris Reimann, MD, share tips for Retisert-related surgery and discuss their approach with a RETINAWS panel.



Thomas Aaberg Jr, MD, shares a case involving Retisert with RETINAWS panel.
bit.ly/RETISERT



Chris Reimann, MD, reviews pearls for the management of a complication in a patient with Retisert.
bit.ly/RETISERT2

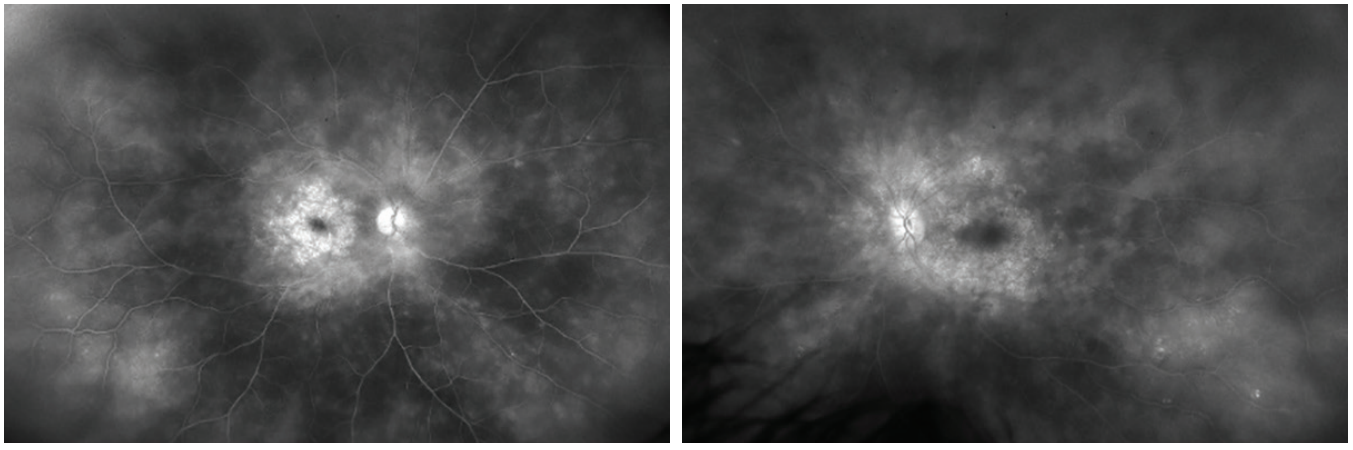


Figure 1. Baseline fluorescein angiography of a patient with sarcoid panuveitis in each eye.

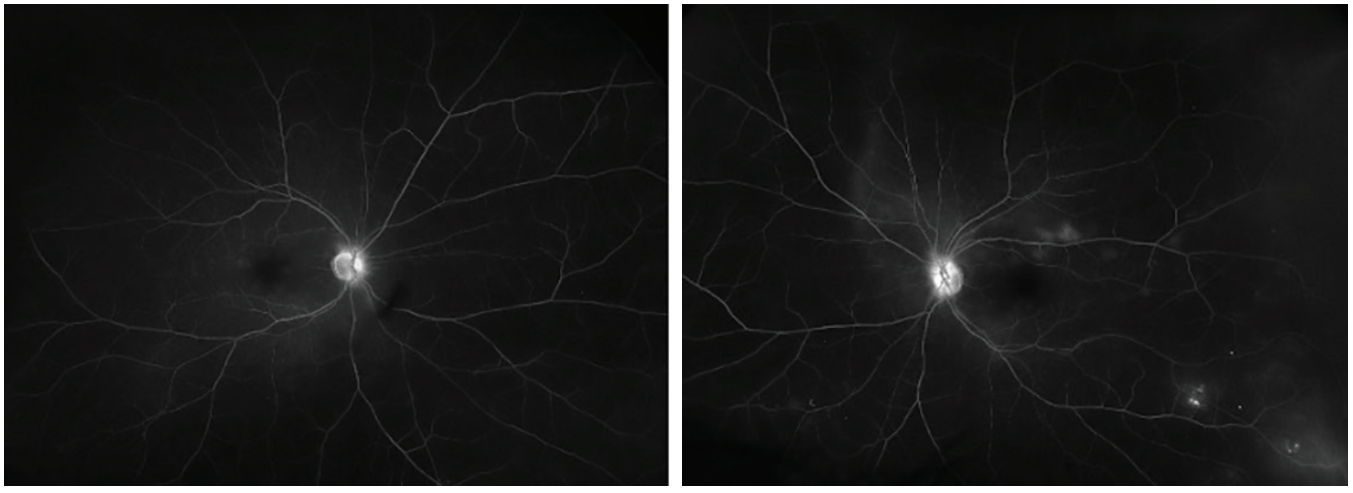


Figure 2. Nine months after therapy was initiated with the fluocinolone acetonide intravitreal implant 0.18 mg, disease resolution was observed.

CASE EXAMPLE

A 47-year-old woman presented with sarcoid panuveitis in both eyes (Figure 1). The patient began therapy with difluprednate ophthalmic emulsion 0.05% (Durezol, Novartis) four times a day OU, prednisone taper starting at 60 mg, and adalimumab 40 mg (Humira, AbbVie) every 2 weeks. At 1 month, while she was receiving high-dose prednisone, her uveitis was well controlled. However, as she tapered the prednisone there were signs of disease recurrence at 2 months follow-up, and oral methotrexate 15 mg daily was added to the regimen.

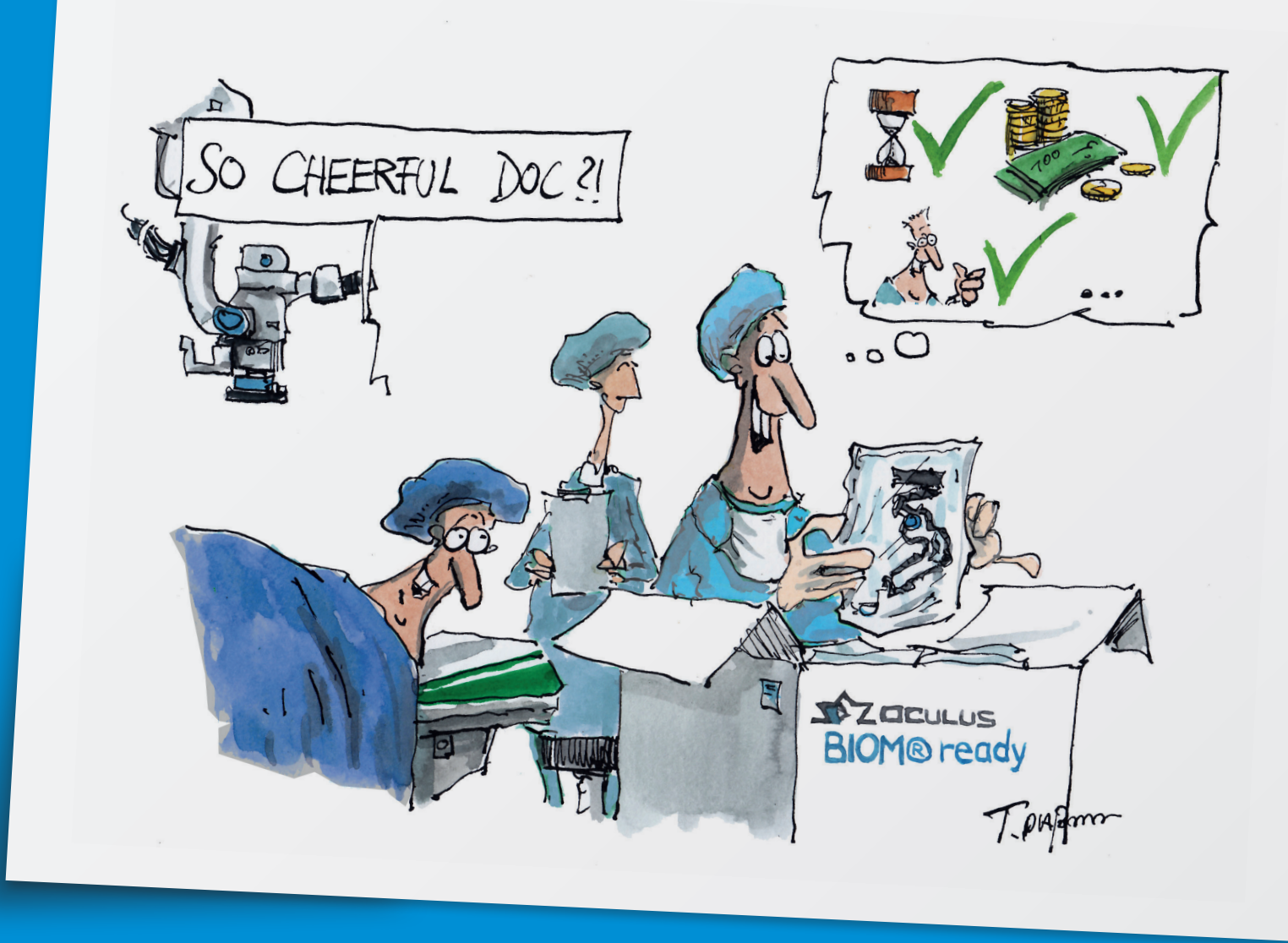
At 6 months, there was still active uveitis. A fluocinolone acetonide intravitreal implant 0.18 mg was administered in each eye. At 9 months, the patient's disease demonstrated significant resolution (Figure 2).

WRAP-UP

This case highlights the value of long-term sustained-release local steroid therapy for the treatment of NIU-PS. This therapeutic approach can be considered in patients who require recurrent local therapy, who have an incomplete response to systemic immunomodulatory therapy, or who need to discontinue immunomodulatory therapy secondary to intolerance or contraindications. ■

1. Jaffe GJ, Pavesio CE, Study Investigators. Effect of a fluocinolone acetonide insert on recurrence rates in noninfectious intermediate, posterior, or panuveitis: three-year results. *Ophthalmology*. 2020;127(10):1395-1404.
2. Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group; Kempen JH, Altaweel MM, Holbrooke JT, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. *Ophthalmology*. 2011;118(10):1916-1926.
3. Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group; Kempen JH, Altaweel MM, Holbrook JT, et al. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA*. 2017;317(19):1993-2005.
4. Albini T, Callaway NF, Jaffe GJ, et al. MUST beg to differ. *Ophthalmic Surg Lasers Imaging Retina*. 2019;50(5):266-268.
5. Jaffe GJ. Reimplantation of a fluocinolone acetonide sustained drug delivery implant for chronic uveitis. *Am J Ophthalmol*. 2008;145(4):667-675.

SUMIT SHARMA, MD
- Assistant Professor of Ophthalmology, Cole Eye Institute, Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio
- sumitsharma.md@gmail.com
- Financial disclosure: Consultant (Genentech/Roche, Regeneron, Bausch + Lomb, Alimera, Allergan, Eyepoint, Clearside); Contracted Research (Gilead, Genentech/Roche, Eyepoint, Kodiak, Ionis, Santen)



OCULUS BIOM® ready

The only non-contact single-use wide-angle viewing system

- **Improve O.R. efficiency**
- **Incorporates the BIOM® HD Disposable Lens for unparalleled clarity and improved depth of field**
- **Uncompromised performance you have come to expect from the OCULUS BIOM®**
- **The perfect balance between flexibility and high optical quality**

Click here to learn more

OCULUS® SURGICAL

Three Pearls for Surgery in Uveitis Patients

Addressing these important questions can help to ensure a positive outcome.

BY LISA J. FAIA, MD

The main indications for surgical intervention for patients with uveitis are the same as those for any patient: to correct a visually significant or vision-threatening etiology. Additionally, interventions may be helpful to elicit a diagnosis or as a form of inflammatory control.

The keys to success with any surgery include a thorough preoperative evaluation, an accurate diagnosis, a proper surgical plan, and a meticulous approach. For surgery in patients with uveitis, additional steps include good preoperative control of the inflammation and a plan for escalation of inflammatory control before surgery to better ensure success. Postoperatively, surgeons must be ready to recognize, as early as possible, any reactivation of inflammation and treat it to ensure that it does not escalate beyond control.

This article discusses three questions you must address before operating on a patient with uveitis:

1. How much do you have to peel if a retinectomy is ultimately necessary?
2. When is "quiet enough" enough for surgery?
3. Is escalation of immunomodulation always needed before surgery?

HOW MUCH DO YOU NEED TO PEEL?

When a patient with uveitis presents with a retinal detachment, whether tractional, rhegmatogenous, or combined, surgeons often recognize that a retinectomy may be necessary. This is particularly common for retinal detachments associated with acute retinal necrosis. The retina is thin and tenacious and, even under perfluorocarbon liquid (PFCL) or sodium hyaluronate (Healon GV, Johnson & Johnson), it remains contracted. Determining how best to perform the retinectomy—where to cut, how much retina is viable—can be a challenge.

The surgeon should start posteriorly, peeling as much as possible to preserve the retina and to avoid leaving a platform for continued inflammation. Peeling as much as possible before cutting also allows the surgeon to use the traction as a "third hand" to create countertraction for further delamination of membranes.

Sodium hyaluronate is a useful tool for countertraction, as it shows the location of the remaining retinal contraction and it can be easily removed, even if it goes subretinal.

In uveitic patients, bleeding is the enemy, even more so than in noninflammatory detachments. The inflammation is an issue, and hemostasis must be achieved (Figure). To watch a successful retinal detachment repair in a patient with uveitis, visit bit.ly/FAIA1.

HOW QUIET DOES THE EYE HAVE TO BE?

In an ideal world, the eye would be completely quiet—meaning no cell, haze, macular edema, vasculitis, etc.—for 3 full months prior to surgery. One of the most common structural complications of uveitis is macular edema.[1-3] Unfortunately, this may represent permanent damage, and it may never fully resolve. Thus, surgeons should reduce macular edema as much as possible before surgery, even though

AT A GLANCE

- When peeling membranes in a uveitic eye, start posteriorly and peel as much as possible to preserve the retina and avoid leaving a platform for continued inflammation and scar tissue formation.
- Prior to surgery, reduce macular edema as much as possible, even though it may be difficult to appreciate the full extent of the edema.
- Once the eye has been quiet for 3 months without escalation of therapy, consider adding prophylactic immunomodulation before proceeding to surgery to avoid future pitfalls.

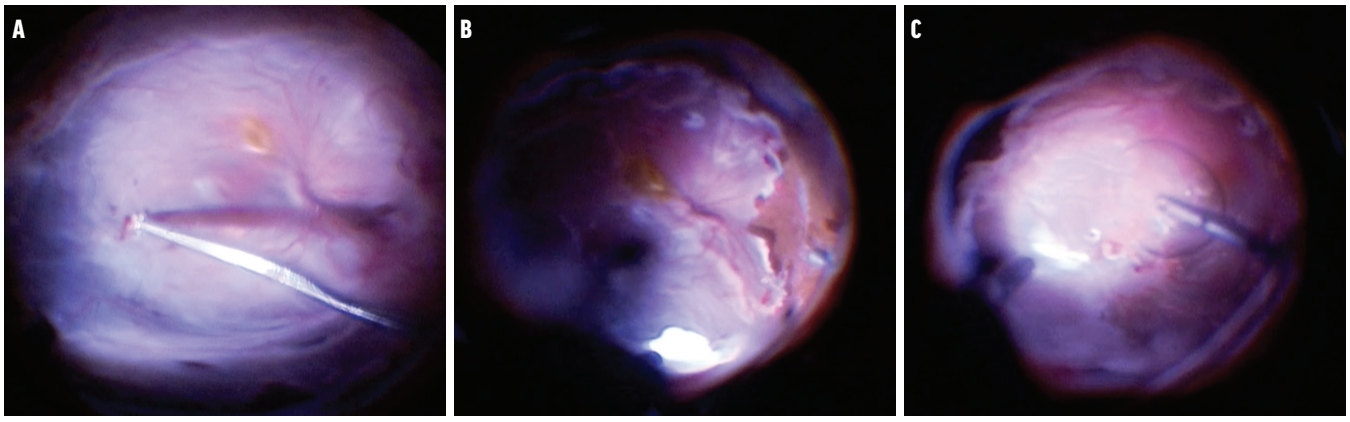


Figure. A 50-year-old woman who developed a combined tractional/rhegmatogenous retinal detachment after stopping her immunomodulation underwent a penetrating keratoplasty and retinal detachment repair. After a temporary keratoprosthesis, a funnel detachment is seen and forceps are used to delaminate the anterior membranes (A). After extensive peeling, a retinectomy is performed while sodium hyaluronate remains in place (B). After the retinectomy, the sodium hyaluronate is removed, PFCL is inserted into the eye, and the retina flattens (C).

it may be difficult to appreciate the full extent and meaning of the edema. Because systemic immunomodulation, other than oral prednisone, requires at least 4 to 6 weeks to take effect, surgery before 6 weeks would be premature.

There are times when surgeons must operate on a "hot eye," such as for endophthalmitis, retinal detachment, or diagnostic vitrectomy. In these instances, surgeons must proceed cautiously and make every effort preoperatively, perioperatively, and postoperatively to eliminate inflammation. No significant cell or haze should be present.

IS ESCALATION OF IMMUNOMODULATION NEEDED?

Once the eye has been truly quiet for 3 months without any escalation of therapy, surgeons should consider adding prophylactic immunomodulation before surgery to avoid future pitfalls. The amount of escalation does not have to be profound—consider starting with a one-step increase above what the patient needs for quiescence. For example, if a patient needs only topical therapies for control, a preoperative or perioperative sub-Tenon injection of triamcinolone or intravitreal injection of preservative-free triamcinolone or a dexamethasone implant may be all that is required. If steroid injections are not plausible, as is the case for glaucoma patients and steroid-responders, consider oral steroids, usually 0.5 mg/kg started 3 days before surgery and tapered by 5 mg to 10 mg each week until the patient is back to baseline.

For patients on systemic medications there are two prophylactic treatment options:

1. Temporarily increase their systemic immunomodulation at least 4 weeks before surgery, maintain the increased amount for at least 3 months after the procedure, and then taper down to the original amount, or
2. prescribe oral steroids if this is an option. Usually, patients do not require more than 60 mg oral prednisone. Again, generally start 3 days before surgery and taper by 5 mg to 10 mg each week postoperatively.

In addition to the patient's current antiinflammatory regimen, there are other factors to consider when discussing a preoperative increase in immunomodulation. For example, the extent of the surgery plays into the formula. The amount of preoperative protection for cataract surgery may be less extensive than that for an epiretinal membrane peel or retinal detachment repair in the same eye.

Beware, however: Even if the patient's uveitis has been quiet for years, preoperative protection against inflammation is worthwhile because even minimal manipulation can cause a reactivation.

TAKEAWAYS

Caring for a patient with uveitis can be challenging, and when a surgical intervention is necessary the disease can be even more difficult to handle. These cases require meticulous care before, during, and after retinal procedures. When it comes to quiescence, be patient; when it comes to preventing postoperative inflammation, be aggressive. ■

1. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. *Br J Ophthalmol*. 1996;80:332-336.
2. Tomkins-Netzer O, Talat L, Bar A, et al. Long-term clinical outcome and causes of vision loss in patients with uveitis. *Ophthalmology*. 2014;121:2387-2392.
3. Nussenblatt RB. The natural history of uveitis. *Int Ophthalmol*. 1990;14:303-308.

LISA J. FAIA, MD
- Vitreoretinal Surgeon, Associated Retinal Consultants, PC, Royal Oak, Michigan
- Associate Professor of Ophthalmology, Co-Director, Uveitis Service, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan
- lfaia@arcpc.net
- Financial disclosure: Advisory Board (AbbVie, Allergan, Genentech, Bausch + Lomb, EyePoint Pharmaceuticals); Speaker (AbbVie, Allergan, Genentech)

Editor's Note: This manuscript is based on "That's Not How the Force Works: Uveitis Surgical Pearls," presented at VBS 2021: The Force Awakens on April 14, 2021.

14 TIPS FOR SCLERAL SUTURING FOR ANY IOL

A good technique for repositioning a dislocated lens can be adapted to many designs.

BY WILLIAM E. SMIDDY, MD

As IOL designs and cataract surgical techniques have evolved, so have the strategies for managing a dislocated lens.

The earliest dislocated posterior chamber (PC) IOLs were often in the context of a ruptured central posterior capsule but without extensive zonular loss. Thus, repositioning commonly involved retrieving the IOL and placing its haptics in the ciliary sulcus. Other management approaches included exchanging the PC IOL for an anterior chamber IOL or using iris fixation sutures.[1]

Repositioning techniques using scleral sutures were developed in the late 1980s and multiplied in the 1990s.[2] The increased variety of these techniques was likely due to broader or more frequent zonular loss, perhaps as a consequence of techniques to allow capsular bag fixation, including endocapsular phacoemulsification and hydrodissection. These fixation techniques were developed and applied in parallel with secondary IOL insertion or IOL exchange, and certain IOLs were even designed with this goal in mind.

The most recent advances in repositioning techniques include the sutureless Yamane procedure[3] and the use of polytetrafluoroethylene (PTFE; Gore-Tex, W.L. Gore) sutures for four-point fixation of an Akreos IOL (Bausch + Lomb).[4]

Although these are important advances, IOL exchange can still be a lengthy procedure that can jeopardize corneal clarity, especially in patients with a history of corneal decompensation or keratoplasty. It may also be more challenging in patients who have undergone prior filtration surgery and therefore have limited residual virgin conjunctiva to work with.

Many, if not most, IOLs are amenable to scleral suture fixation with relatively simple modifications to a long-standing technique (Figure 1).

Here are 14 pearls to help you optimize this technique and modify it to accommodate a wide range of IOL styles.

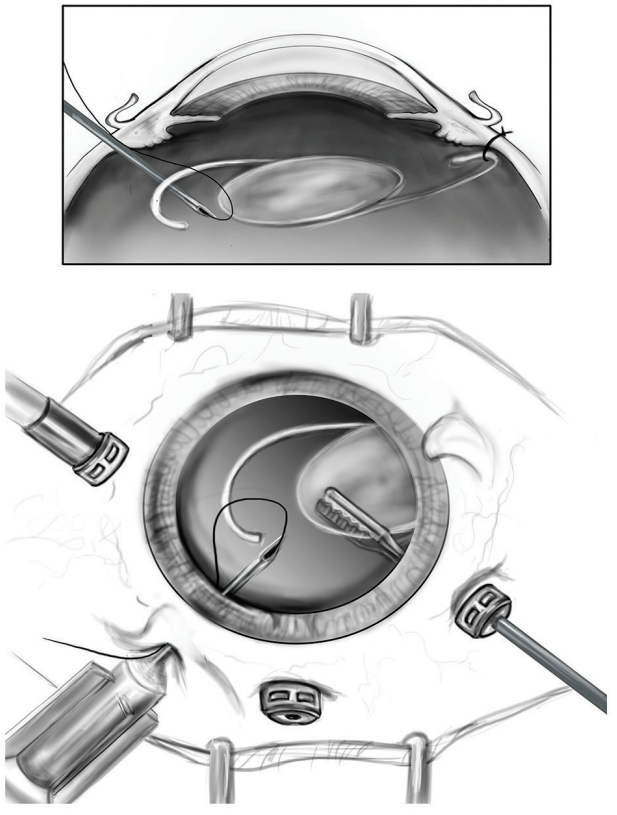


Image courtesy of Sepideh Omidghaemi, OD

Figure 1. With a little ingenuity, this scleral suture technique can be easily adapted to most types of IOLs.

1. RESPECT THE CONJUNCTIVA

Preserve the continuity and integrity of this structure as if you were a glaucoma surgeon. The old adage that every step depends upon the successful completion of the previous step is true, and in this case the first step is ensuring that you have a good conjunctival site or that you adjust your incisions to optimize what conjunctiva remains.

2. MAKE THE RIGHT FLAP

Prepare a 50% to 75% thickness scleral flap to allow you to bury the knot and the bulk of the fixation suture; don't make the flap too thin. I prefer a triangular, limbus-based construction. The flap always seems to be smaller than you would

expect, so an obtuse triangle with a broad base will leave more covering tissue.

3. PREPARE AND PLACE CONVENIENT FIXATION SITES

Ergonomically, it is most convenient to place the fixation sites at the 1:30 and 7:30 meridians, but site constraints might dictate otherwise. Either way, place the two sites 180° from each other to avoid difficulties with IOL centration.

4. SET THE STAGE OPTIMALLY

Perform a complete vitrectomy, unless it will jeopardize a more convenient retrieval with forceps when the IOL is still suspended anteriorly. If the IOL is completely dislodged and rests on the retina, elevate it using the vitrectomy machine on suction mode, which is safer than trying to grasp the IOL with forceps.

5. USE A THICK SUTURE AND A THIN NEEDLE

There has been concern that polypropylene sutures will degrade with time, which would be particularly problematic in a young patient. However, using 9-0 rather than 10-0 polypropylene avoids this complication. A 27-gauge needle is small enough to minimize postoperative leaking, but large enough to handle the polypropylene suture.

6. WATCH OUT FOR THE NEEDLE

Introduce the suture by threading it retrograde through the base of the flap, but take care to keep the needle end of the suture in front of the needle bevel to avoid amputating it during entry.

7. PLACE FIXATION POSTERIOR

Introduce the needle 3 mm posterior to the limbus. I used to aim 1 mm posterior to the limbus, striving to guide the haptic into the sulcus. Newer techniques, however, have demonstrated that IOLs are well tolerated slightly more posterior, and this positioning offers the benefit of less iris chafing and less refractive change, as it approximates the positioning of the originally intended bag fixation.

8. LOOP THE INFERIOR HAPTIC FIRST

Once the inferior haptic is secured to the suture, the IOL hangs down so that you can reach the remaining haptic. If you do it the other way, it is difficult to find and manipulate the haptic, which is often obscured from view by the superior iris. Also, make sure the haptic orientation is accurate at this point.

9. GENERATE SLACK WHEN LOOPING THE HAPTIC

Grasp the edge of the optic with intraocular forceps (mild impression marks usually resolve) to direct the haptic into the suture loop, rather than trying to lasso the haptic with the suture (Figure 2). It helps to generate some slack to make the loop, which can be done by inserting the needle maximally and then retracting it slightly. The suture will not come out of the sclera as much as the needle, leaving a convenient space between the needle shaft and the suture through which the haptic can be inserted.

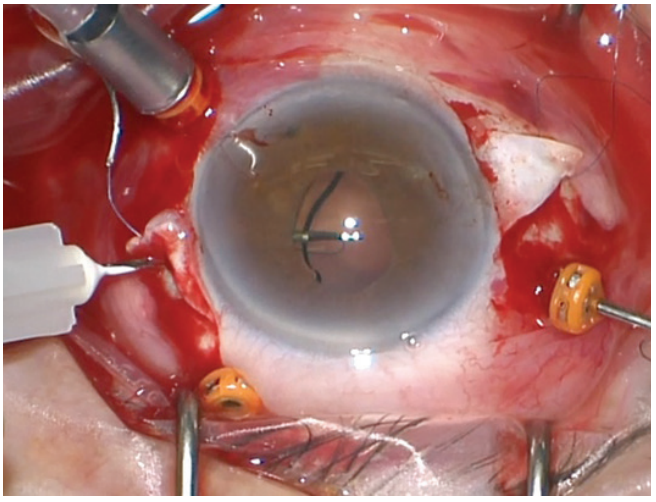


Figure 2. Sometimes, rather than lassoing the haptic, you can create the suture loop first, then thread the haptic through; this image shows a one-piece acrylic IOL.

10. FIXATE THE SUTURE TO THE HAPTIC SEPARATELY

Tie a knot snugly (but not too tight) so that the suture is attached to the IOL haptic. Subsequently, use a partial thickness pass to secure it to the sclera, providing room for adjustment of the IOL positioning (allowing the knot to prolapse internally) to optimize centration.

11. LEAVE LONG SUTURE ENDS

Doing this will help the ends lie flatter, presenting a less pointy profile to the conjunctiva. This lessens the risk of erosion, even if the suture ends extend beyond the edge of the scleral flap.

12. TAKE CARE WITH CONJUNCTIVAL CLOSURE

Again, channel your favorite glaucoma surgeon to avoid a fistula, retraction, or buttonhole.

13. MAXIMIZE THE VIEW

Don't hesitate to use iris hooks or an expander in the presence of small pupils. Generally, this is necessary only if the pupil is less than 2 to 3 mm in diameter.

14. INSPECT THE RETINA

Iatrogenic tears or mobilized capsular or cortical remnants are easily addressed before closing.

SUTURING TIPS IN PRACTICE

The ideal IOL design for scleral suture repositioning is a three-piece IOL. However, the basic framework discussed

(Continued on page 48)

A RARE MANIFESTATION OF CHRONIC MYELOGENOUS LEUKEMIA

This condition should remain in the differential when a patient presents with signs of ocular ischemic syndrome.

BY MICHAEL WEAVER, DO; SAMIR DALIA, MD; AND HEERAL R. SHAH, MD

CASE

A 57-year-old man was referred to the retina clinic by his primary care provider for a routine diabetic eye examination. He had no visual complaints and no history of retinal pathology. He had attended annual diabetic eye examinations for the past 12 years.

His medical history was notable for type 1 diabetes with no insulin requirement and hyperlipidemia. He had undergone a pancreatic transplant in 2015 due to uncontrolled diabetes and islet cell dysfunction. Since his transplant, his hemoglobin A1C had normalized, and he was instructed to stop taking oral diabetic medication. His ocular history was significant for cataract surgery in each eye in 2017.

Examination revealed UCVA of 20/25 OD and 20/15 OS, normal IOPs, and well-centered IOLs. Dilated fundus examination revealed asteroid hyalosis in the right eye, clear vitreous in the left eye, and healthy nerves with a cup-to-disc ratio of 0.3 in each eye. Both eyes had prominent arteriovenous nicking changes, diffuse dot-blot hemorrhages in all peripheral quadrants, mild venous engorgement, and neovascularization along the superior and inferior temporal arcades. Rare macular dot-blot hemorrhages were appreciated (Figure 1). Fluorescein angiography revealed delayed arteriovenous filling time, peripheral nonperfusion, several areas of neovascularization leakage, and leaking microaneurysms in the macula (Figure 2). OCT revealed trace macular edema (Figure 3).

At this time, working diagnoses of ocular ischemic syndrome (OIS), venous stasis retinopathy, and delayed-onset proliferative diabetic retinopathy were considered. Bloodwork and a carotid ultrasound were ordered, and the patient was scheduled to return for panretinal photocoagulation.

Before his return for laser treatment, the patient presented to the emergency department due to fatigue and dizziness and was found to have leukocytosis with a white blood cell count of 80,000/mm^3, which was predominately neutrophilia. A peripheral smear in the emergency department showed rare blast forms with a predominance of mature neutrophils suggestive of a myeloproliferative disorder. He was scheduled to see hematology/oncology the next day.

At the oncology clinic, the patient's leukocytosis had increased, with a white blood cell count of 114,000/mm^3 with elevated cells of various progression within the myeloid lineage. No blasts were noted on a peripheral smear.

At that time, the patient was given a presumptive diagnosis of chronic myelogenous leukemia (CML), peripheral blood was drawn for a Philadelphia chromosome (BCR-ABL PCR) test, and the patient was started on hydroxyurea to lessen the chance of leukostasis. Bone marrow biopsy revealed left-shifted myeloid hyperplasia with no increase in blast cells or evidence of abnormal lymphoid or plasma cell populations. Philadelphia chromosome translocation was seen in all cells, consistent with CML. The patient was started on dasatinib (Sprycel, Bristol Myers Squibb), and improvement of his BCR-ABL percentage, clinical symptoms, and blood counts followed. The patient completed panretinal photocoagulation and is being followed to see if the retinal findings resolve.

DISCUSSION

OIS is a rare condition stemming from prolonged ocular hypoperfusion. Mean age at onset is 65 years, it is twice as common in men as women, and there is bilateral involvement in up to 22% of cases.[1,2] The incidence is estimated to be 7.5 per million, although this number may be artificially low as OIS is frequently misdiagnosed. There is a high 5-year mortality rate associated with OIS, especially due to cardiovascular disease.[2]

The term *venous stasis retinopathy* describes the posterior segment findings of OIS, such as retinal artery narrowing

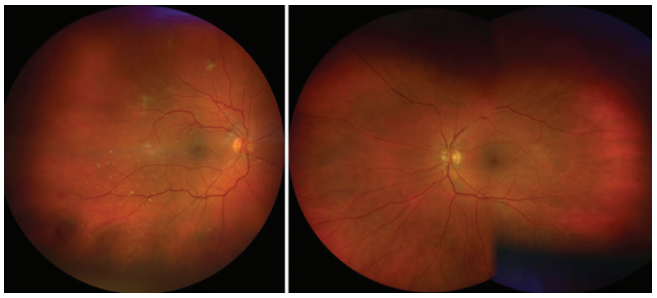


Figure 1. Fundus photography showed asteroid hyalosis in the right eye.

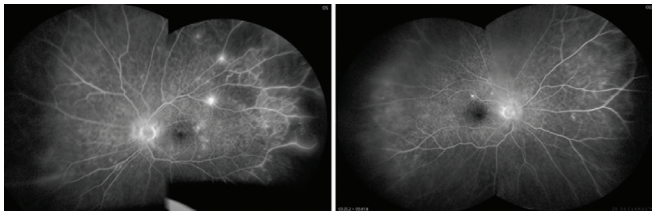


Figure 2. Fluorescein angiography revealed several findings, including delayed arteriovenous filling time, peripheral nonperfusion, neovascularization leakage, and leaking microaneurysms in the macula.

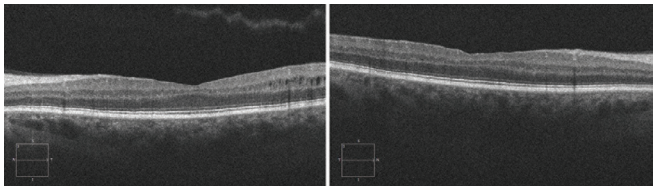


Figure 3. OCT showed trace macular edema in each eye.

and retinal vein dilation.[3] Retinal hemorrhages, usually in the external layers in the midperiphery, small in number and rarely confluent, are characteristic and seen in 80% of affected eyes.[1] Microaneurysms are frequently seen in both the macula and the midperiphery.

Among the first manifestations of OIS are diffuse macular capillary telangiectasias that, combined with microaneurysms, lead to macular edema. Neovascular glaucoma may lead to quick progression of optic disc damage, though this may also be due to ischemia of the optic disc and reduction of retrobulbar blood flow.[1] Ischemia of the retina may also lead to increased production of VEGF. Neovascularization may occur, more often at the optic disc than the retina, which may lead to vitreous hemorrhages. Other signs of OIS include cotton-wool spots, chorioretinal atrophy, choroidal neovascular membrane, and anterior or posterior ischemic optic neuropathy.[1]

In 90% of patients, OIS will present with vision loss, usually related to chronic or acute retinal ischemia or damage to the optic nerve from secondary glaucoma.[1] Vision loss is often gradual, with 67% of patients experiencing loss over weeks to months. Although many patients will present with relatively good vision—43% with a VA of 20/20 to 20/50—after 1 year of follow-up, 58% of all eyes will have VA ≤ counting fingers.[4]

Anterior segment signs are not uncommon in OIS. Roughly 66% of patients will experience neovascularization of the iris and iridocorneal angle; however, only 50% will have elevated IOP or neovascular glaucoma.[1]

Fluorescein angiography in OIS will demonstrate a prolonged arm-to-choroid and arm-to-retina circulation time, with the affected eyes in 60% of patients taking a minute or longer to fill. The most sensitive sign is prolonged retinal arteriovenous time, present in 95% of cases. This, however, is nonspecific. Staining of major retinal vessels and their branches in late phase angiography is seen in 85% of eyes, possibly due to endothelial cell damage secondary to chronic ischemia.[1]

The differential diagnosis of OIS includes occlusion of either the internal or common carotid artery, carotid aneurysm, giant cell arteritis, fibrovascular dysplasia, inflammatory conditions, diabetic retinopathy, and central retinal vein occlusion (CRVO).[2,5,6] OIS, unlike CRVO, does not present with dilated and tortuous retinal veins. OIS may be differentiated from diabetic retinopathy by an absence of hard exudates and fewer retinal hemorrhages. Neither CRVO nor diabetic retinopathy show retinal arterial stasis or choroidal filling defects.[1] Additionally, the differential diagnosis for OIS should include hyperviscosity syndromes and autoimmune uveitis, which may be seen in hematologic and oncologic disorders.

Uncommonly, the retina can be infiltrated by neoplastic cells and affected by anemias and hyperviscosity syndromes associated with leukemia. Leukemic retinopathy (present in 36% to 50% of newly diagnosed acute myeloid leukemia patients) may present with intraretinal hemorrhages (24%), white-centered retinal hemorrhages (11%), and cotton-wool spots (16%).[7]

Extreme leukocytosis, as was seen in our patient, can lead to peripheral nonperfusion and neovascularization. In a review of chronic leukemias, prolonged leukocytosis was associated with vascular stagnation, peripheral capillary dropout, microaneurysm formation, and, rarely, proliferative retinopathy.[8] That review included no patients with proliferative retinopathy, which the authors noted was likely due to maintenance of leukocyte counts under 50,000/mm^3. There are, however, two notable studies of CML leading to proliferative retinopathy with a striking resemblance to sickle cell retinopathy.[9,10]

Treatment of ocular manifestations of leukemia builds on systemic modalities such as chemotherapy and biologic therapies.[11] Because systemic therapies may not be adequate due to poor penetration to ocular structures, local therapeutic approaches including intravitreal injections of dexamethasone, anti-VEGF agents, or methotrexate have been investigated.[11] Intravitreal methotrexate is thought to be effective as an adjunctive treatment in the absence of systemic active disease in the blood or bone marrow, based on a small investigation.[11]

Treatment of OIS is often complex and multifactorial. Although visual changes associated with OIS are often irreversible, it is important to treat the associated excessive VEGF production. Ablation of the peripheral retina via panretinal

photocoagulation is indicated in patients with neovascularization in the anterior or posterior segment; however, this is effective in only 36% of patients because choroidal ischemia alone is enough to prompt production of VEGF.[1]

Additionally, elevated IOP should be treated with topical IOP-lowering therapy and may require a glaucoma specialist to comanage, especially for patients who develop neovascular glaucoma.

CONCLUSION

For all patients with OIS, a multidisciplinary approach is necessary to find the underlying etiology, especially given the high mortality rates associated with this condition. Although the most common cause is carotid occlusion, hematologic malignancies must remain in the differential diagnosis. It is unlikely that vision losses associated with OIS can be completely reversed, so preventing progression is the main target of therapy. ■

1. Terelak-Borys B, Skonieczna K, Grabska-Liberek I. Ocular ischemic syndrome - a systematic review. *Med Sci Monit*. 2012;18(8):RA138-RA144.
2. Mendrinos E, Machinis TG, Pournaras CJ. Ocular ischemic syndrome. *Surv Ophthalmol*. 2010;55(1):2-34.
3. Duker JS, Magargal LE, Stubbs GW. Quadrantic venous-stasis retinopathy secondary to an embolic branch retinal artery obstruction. *Ophthalmology*. 1990;97(2):167-170.
4. Sivalingam A, Brown GC, Magargal LE. The ocular ischemic syndrome. III. Visual prognosis and the effect of treatment. *Int Ophthalmol*. 1991;15(1):15-20.
5. Brown GC, Magargal LE. The ocular ischemic syndrome. Clinical, fluorescein angiographic and carotid angiographic features. *Int Ophthalmol*. 1988;11(4):239-251.
6. Mizener JB, Podhajsky P, Hayreh SS. Ocular ischemic syndrome. *Ophthalmology*. 1997;104(5):859-864.
7. Talcott KE, Garg RJ, Garg SJ. Ophthalmic manifestations of leukemia. *Curr Opin Ophthalmol*. 2016;27(6):545-551.
8. Jampol LM, Goldberg MF, Busse B. Peripheral retinal microaneurysms in chronic leukemia. *Am J Ophthalmol*. 1975;80(2):242-248.
9. Morse PH, McCready JL. Peripheral retinal neovascularization in chronic myelocytic leukemia. *Am J Ophthalmol*. 1971;72(5):975-978.
10. Frank RN, Ryan SJ Jr. Peripheral retinal neovascularization with chronic myelogenous leukemia. *Arch Ophthalmol*. 1972;87(5):585-589.
11. Vishnevskia-Dai V, Sella King S, Lekach R, Fabian ID, Zloto O. Ocular manifestations of leukemia and results of treatment with intravitreal methotrexate. *Sci Rep*. 2020;10(1):1994.

SAMIR DALIA, MD
- Hematologist Oncologist, Mercy Clinic Joplin, Joplin, Missouri
- Associate Professor of Internal Medicine, Kansas City University of Medicine and Biosciences, Kansas City, Missouri
- samir.dalia@mercy.net
- Financial disclosure: None

HEERAL R. SHAH, MD | SECTION EDITOR
- Retina Specialist, Ramesh R. Shah, MD, PC, Joplin, Missouri
- Assistant Professor, Kansas City University of Medicine and Biosciences
- Co-Founder, International Society for the Advancement of Medical Retina
- heeralshahmd@gmail.com
- Financial disclosure: Consultant (Allergan, Genentech)

MICHAEL D. WEAVER, MD
- Post-Graduate Year 1 Pharmacy Resident, Internal Medicine, Freeman Health System, Joplin, Missouri
- mdweaver@kansascity.edu
- Financial disclosure: None

(Continued from page 45)

here may apply to other IOL types. With a toric IOL, for example, the location of the flaps (ie, fixation meridian) can be adjusted to optimize postoperative correction. On one-piece acrylic IOLs such as the AcrySof SA60 (Alcon), the ends are thicker than the middle of the haptics, and this feature often allows them to be repositioned using the steps described here.[5]

Other one-piece IOL designs, such as the Tecnis Symfony (Johnson & Johnson Vision), feature tapered haptics, but there is often a notch at the haptic-optic junction around which the suture can be looped.[6]

Certain IOLs, such as the Crystalens (Bausch + Lomb), have much larger haptics. With the help of forceps or a needle, you can free up additional suture slack internally to allow easy lassoing of even these large haptics.

Finally, adapting the PTFE suture method,[4] a four-loop Akreos IOL can be scleral-fixated with polypropylene suture instead, albeit with slightly more internal maneuvering.[7] In this instance, the suture is introduced through a partial thickness scleral slit approximately 2 clock hours beyond the flap, through the superior hole, then retrieved with 25-gauge forceps through the scleral flap bed, inserted through the inferior hole, and externalized. The needle end is then passed through partial scleral thickness counterclockwise from the slit to the flap, where the united ends can be sutured while the tension is adjusted to allow IOL centration.

Respecting the basics of good technique in scleral suture fixation for dislocated IOLs will help you to maximize results not only for the IOLs typically encountered, but for an expanded variety of lens designs. ■

1. Stark WJ, Michels RG, Bruner WE. Management of posteriorly dislocated intraocular lenses. *Ophthalmic Surg*. 1980;11(8):495-497.
2. Kim SS, Smiddy WE, Feuer W, Shi W. Management of dislocated intraocular lenses. *Ophthalmology*. 2008;115(10):1699-1704.
3. Yamane S, Sato S, Maruyama-Inoue M, Kadonosono K. Flanged intrascleral intraocular lens fixation with double-needle technique. *Ophthalmology*. 2017;124(8):1136-1142.
4. Patel NA, Shah P, Yannuzzi NA, et al. Clinical outcomes of 4-point scleral fixated 1-piece hydrophobic acrylic equiconvex intraocular lens using polytetrafluoroethylene suture. *Clin Ophthalmol*. 2018;12:2145-2148.
5. Leung EH, Mohsenin A, Smiddy WE. Scleral suture fixation technique for one-piece acrylic intraocular lens. *Retina Cases Brief Rep*. 2018;12(3):251-253.
6. Echegaray JJ, Smiddy WE. Scleral suture fixation of dislocated posterior chamber intraocular lens: modification for tapered haptics. Published online June 29, 2020. *Retina*.
7. Fan KC, Smiddy WE. Rescuing an Akreos 4-point haptic intraocular lens: a novel surgical technique. Published online March 3, 2021. *Retina*.

WILLIAM E. SMIDDY, MD
- Professor of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami
- wsmiddy@med.miami.edu
- Financial disclosure: None

INGRID SCOTT, MD, MPH | SECTION EDITOR
- Professor of Ophthalmology and Public Health Sciences, Penn State Eye Center, Penn State College of Medicine, Hershey, Pennsylvania
- Editorial Advisory Board Member, *Retina Today*
- Financial disclosure: None

Euretina 2021

EURETINA
European Society of Retina Specialists

VIRTUAL
9-12 September

4 Days. 5 Channels

Keynote Lectures

Euretina Lecture
SriniVas Sadda *USA*
Choriocapillaris in AMD: New Insights into Pathophysiology

Gisbert Richard Lecture
Heinrich Heimann *UK*
Visual Acuity Following Retinal Detachment Surgery

Kreissig Award Lecture
Ogugua Okonkwo *NIGERIA*
Neuroprotective Strategy for Non-Arteritic Central Retinal Artery Occlusion

Ophthalmologica Award Lecture
Camiel Boon *THE NETHERLANDS*
Serous Business: Dissecting The Broad Spectrum of Diseases With Subretinal Fluid in the Macula

Programme and Registration
information available on the website **www.euretina.org**

UVEAL MELANOMA CLASSIFIED BY THE CANCER GENOME ATLAS


This new system can help identify patients at high risk for metastasis, possibly paving the way for targeted adjuvant therapy.

BY ZEYNEP BAS, MD, AND CAROL L. SHIELDS, MD

Uveal melanoma is a life-threatening condition leading to systemic metastasis in approximately 25% to 40% of patients by 10 years.[1,2] Metastatic disease most often occurs in the liver (89%), followed by lung (29%), bone (17%), and skin (12%).[3] In the past, certain clinical and pathologic features of melanoma were shown to be predictive of metastasis, including large tumor size, ciliary body location, diffuse configuration, and histopathologic factors (Figure). More recently, genetic markers have helped to predict prognosis.[4]

The Cancer Genome Atlas (TCGA) is an international project conceived by the US National Cancer Institute and the National Human Genome Research Institute for the investigation of various mutations in different types of cancers.[5-7] This team studied 33 human tumors, including uveal melanoma, and profiled them by DNA, RNA, and protein and epigenetic alterations.

UVEAL MELANOMA CLASSIFIED

TCGA was used to evaluate a relatively small cohort of 80 eyes with uveal melanoma at the US National Institutes of Health (NIH). The multiplatform analysis, using chromosome copy number alterations, DNA methylation status, RNA expression, protein translation, and immune markers, provided a basic four-group classification (Table 1).[4] Subsequently, a simplified, or practical, form of this classification, based on DNA alterations alone, allowed researchers to categorize uveal melanoma into four prognostic groups (Table 2): Group A (chromosome 3 disomy, chromosome 8 disomy), Group B (chromosome 3 disomy, chromosome 8q gain), Group C (chromosome 3 monosomy), and Group D (chromosome 3 monosomy, chromosome 8q multiple gain).[8]

UVEAL MELANOMA OUTCOMES

In 2019, our team published a validation of the practical TCGA classification of uveal melanoma in 658 consecutive cases. All patients had genetic testing of the tumor for chromosomes 3 and 8.[9] The study data revealed that prognosis directly correlated with TCGA group, and the 5-year rate of metastasis increased significantly ($P < .001$) for each group: 4% for Group A, 20% for Group B, 33% for Group C, and 63% for Group D. Thus, TCGA was highly predictive of metastatic risk in this large cohort.[9]

More recently, we explored 5- and 10-year outcomes following treatment of uveal melanoma using TCGA classification in a cohort of 1,001 eyes with uveal melanoma treated with plaque radiotherapy or enucleation over a 22-year period (Table 3).[10] Outcomes for melanoma-related metastasis and death by Kaplan-Meier analysis demonstrated that the cumulative percentage of distant metastasis significantly

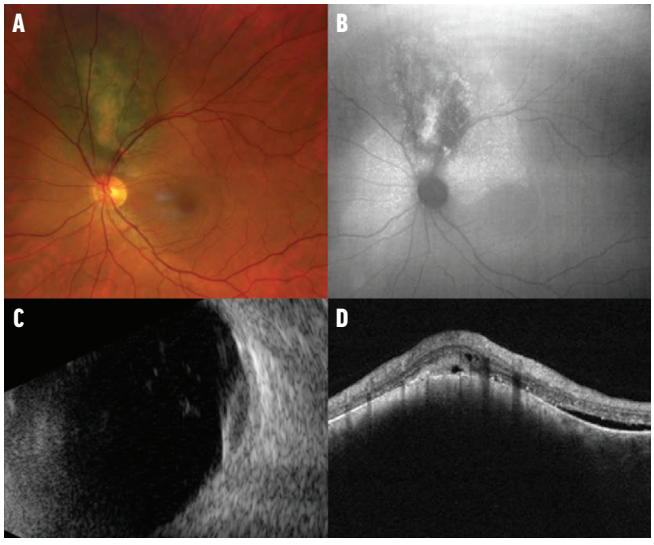


Figure. Fundus imaging shows choroidal melanoma superior to the optic disc in a 49-year-old woman (A). Fundus autofluorescence demonstrates orange pigment in the central part of the tumor (B). B-scan ultrasonography shows characteristic acoustic hollowness (C). OCT overlying the tumor depicts serous retinal detachment (D). This patient had a fine needle aspiration biopsy at the time of plaque radiotherapy for genetic testing, and results came in as chromosome disomy 3, 6, and 8, consistent with TCGA Group A. This low-risk cytogenetic profile suggests a 6% risk for metastasis at 10 years.

TABLE 1. FOUR MOLECULARLY DISTINCT GROUPS OF UVEAL MELANOMA IN 80 EYES, ORDERED BY INCREASING CHROMOSOMAL INSTABILITY

	Group A		Group B		Group C		Group D	
Chromosome 3	Disomy (D3)		Disomy (D3)		Monosomy (M3)		Monosomy (M3)	
Significantly mutated genes	*EIF1AX*		*SF3B1*		*BAP1*		*BAP1*	
DNA methylation profile*	1		2/3		4		4	
mRNA clusters**	1	2	1	2	3	4	3	4
lncRNA clusters**	1	2	1	2	3	4	3	4

Adapted from Robertson AG, Shih J, Yau C, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. *Cancer Cell*. 2017;32(2):204-220.
Abbreviations: mRNA, messenger RNA; lncRNA, long noncoding RNA

*DNA methylation profile was grouped into four clusters, defined by BAP1 gene mutation status. BAP1 loss caused epigenetic downregulation such as DNA methylation. Poor prognosis Groups C and D had 85% BAP1 gene loss causing a global DNA methylation pattern.
**Analysis of mRNA and lncRNA expression levels resulted in four clusters. Loss of BAP1 gene in Groups C and D led to decreased levels of BAP1 mRNA expression. Some well-established cancer-associated lncRNAs were found to be more common in M3 tumor groups compared with D3 tumor groups. Based on these RNA expression profiles, both D3 and M3 tumor groups were further divided into Groups A and B and Groups C and D.

TABLE 2. OVERVIEW OF PROGNOSTIC GROUPS

	Group A	Group B	Group C	Group D
Chromosome 3	Disomy (D3)	Disomy (D3)	Monosomy (M3)	Monosomy (M3)
Chromosome 6	Extra 6p	Extra 6p	-	-
Chromosome 8	Normal 8q	Partial extra 8q	Extra 8q	Extra 8q (multiple)
mRNA clusters*	1	1	2	2
Prognosis	Favorable	Late metastases	Unfavorable	Unfavorable

Adapted from: Jager MJ, Brouwer NJ, Esmaeli B. The Cancer Genome Atlas Project: An integrated molecular view of uveal melanoma. *Ophthalmology*. 2018;125(8):1139-1142.
Abbreviations: mRNA, messenger RNA
*Expression analysis revealed two subgroups for mRNA; tumors with BAP1 gene mutations had low levels of mRNA. These transcriptional clusters trended similarly with the chromosome 3 copy number profiles.

increased based on TCGA group ($P < .001$): 3%, 9%, 20%, and 46%, for Groups A, B, C, and D, respectively. Findings also revealed shorter mean time to distant metastasis (37.4, 38.7, 27.7, and 21.5 months, respectively, $P = .009$) and higher percentage of melanoma-related death (< 1%, 0%, 2%, and 7%, respectively, $P = .003$) at date last seen.[10] Kaplan-Meier analysis showed that advanced TCGA groups were associated with a higher risk for distant metastasis at 5 years (4%, 12%, 33%, and 60%, respectively) and at 10 years (6%, 20%, 49%, and not available, respectively).[10]

CONDITIONAL SURVIVAL

Current survival models estimate a patient's outcome from a single static time point, usually the date of presentation. However, survival probabilities can change over time. A dynamic evaluation of survival, called *conditional survival*, is based on survival per an interval of time. This time-dependent statistical information can help guide counseling and decision-making.

Merrill et al evaluated conditional survival in an impressive cohort of 1,151,496 cancer patients from the Surveillance, Epidemiology, and End Results (SEER) registry and showed that, for patients who lived to 5 years, conditional survival probability exceeded 90% for several cancers, including prostate cancer, melanoma, breast cancer, uterine cancer, bladder cancer, Hodgkin lymphoma, rectal cancer, colon cancer, ovarian cancer, and pancreatic cancer.[11]

In 2020, Zabor et al evaluated metastasis-free survival in 6,863 patients with uveal melanoma and found that nonconditional survival rate was 80% at 5 years, but conditional survival changed.[12] For patients surviving 1, 2, 3, and 4 years, for example, the conditional survival

TABLE 3. EVENT-FREE SURVIVAL ANALYSIS OF METASTASIS AND DEATH IN 1,001 CASES

Outcomes	The Cancer Genome Atlas Group				Total
	Group A n (%)	Group B n (%)	Group C n (%)	Group D n (%)	n (%)
Number of patients	486	141	260	114	1,001
Distant metastasis					
2 Years	315 (98)	92 (97)	118 (85)	52 (64)	577 (91)
5 Years	160 (96)	40 (88)	41 (67)	12 (40)	254 (82)
10 Years	16 (94)	6 (80)	5 (51)	na	27 (75)
Liver metastasis					
2 Years	315 (98)	92 (97)	118 (85)	52 (65)	577 (91)
5 Years	160 (98)	40 (88)	41 (67)	12 (42)	254 (82)
10 Years	17 (96)	6 (80)	5 (55)	na	28 (77)
Melanoma-related death					
2 Years	316 (100)	92 (100)	131 (100)	66 (96)	604 (99)
5 Years	162 (> 99)	41 (100)	42 (93)	14 (85)	259 (97)
10 Years	17 (99)	6 (100)	5 (93)	na	28 (97)

Adapted from Shields CL, Mayro EL, Dockery PW, et al. Ten-year outcomes of uveal melanoma based on the cancer genome atlas (TCGA) classification in 1001 Cases. *Indian J Ophthalmol*. 2021. [In press]. Abbreviations: na, not available

rates at 5 years increased to 82%, 87%, 92%, and 96%, respectively. The 10-year nonconditional survival rate was 69%, whereas the conditional survival rate 5, 6, 7, 8, and 9 years after initial diagnosis increased to 87%, 90%, 93%, 96%, and 98%, respectively.[12]

We used TCGA classification to explore metastatic risk based on conditional analysis (Table 4).[13] We found that patients who survive 5 years with treated uveal melanoma without metastasis showed dramatic reductions in conditional risk for metastasis for Group A (6% at date first seen vs 2% at 5 years), Group B (20% at date first seen vs 10% at 5 years), Group C (49% at date first seen vs 23% at 5 years), and Group D (68% at date first seen vs 20% at 5 years).[13] This suggests that longer survival without metastasis could correlate with an evolving reduction in metastatic risk—an important message to convey to long-term patients. The practical TCGA classification successfully predicted both nonconditional and conditional risk for melanoma-related metastasis and death over time.

CAN WE PREVENT METASTASIS?

Now that we can identify patients at high risk for metastasis, should we treat them with adjuvant chemotherapy to prevent metastasis? Only a few drugs are available that might be beneficial, including tyrosine kinase inhibitors (TKIs), dendritic cell vaccination, and monoclonal T-cell receptors.[14-16]

Sunitinib (Sutent, Pfizer) is an oral TKI that blocks multiple tyrosine kinases including C-kit proto-oncogene, VEGF, and platelet-derived growth factor receptors and can serve as an antitumor and antiangiogenic molecule.[14] Valsecchi et al evaluated 128 patients with high-risk uveal melanoma, 54 of whom received adjuvant sunitinib and 74 of whom served as controls.[14] Low-dose adjuvant sunitinib for 6 months was associated with longer survival time, especially notable in patients 60 years or younger.[14]

Another new class of drugs, immune-mobilizing monoclonal T-cell receptors against cancer (ImmTAC) are being investigated for the treatment of uveal melanoma. Tebentafusp (Immunocore) is the first ImmTAC molecule, a fusion protein engineered to direct cytotoxic T cells toward tumor cells expressing melanocyte lineage-specific antigen, inducing apoptosis.[15] Middleton et al evaluated 84 patients with metastatic skin and uveal melanoma and showed that survival with tebentafusp was 65% at 1 year with metastatic melanoma.[15]

TABLE 4. CONDITIONAL SURVIVAL IN 1,001 CASES

	Duration of achieved event-free survival	The Cancer Genome Atlas Group								Total	
		Group A n (%)		Group B n (%)		Group C n (%)		Group D n (%)		n (%)	
Number of patients		486		141		260		114		1,001	
	Distant metastasis	**5 Years**	**10 Years**	**5 Years**	**10 Years**	**5 Years**	**10 Years**	**5 Years**	**9 Years**	**5 Years**	**10 Years**
Conditional metastasis-free survival	2 years	161 (98)	16 (95)	40 (92)	6 (82)	41 (79)	5 (60)	12 (62)	4 (50)	254 (90)	27 (82)
	3 years	161 (98)	16 (96)	40 (93)	6 (83)	41 (83)	5 (64)	12 (83)	4 (67)	254 (94)	27 (86)
	4 years	161 (99)	16 (96)	40 (98)	6 (88)	41 (88)	5 (68)	12 (94)	4 (75)	254 (97)	27 (88)
	5 years	na	16 (98)	na	6 (90)	na	5 (77)	na	4 (80)	na	27 (91)
	Melanoma-related death	**5 Years**	**10 Years**	**5 Years**	**10 Years**	**5 Years**	**10 Years**	**5 Years**	**9 Years**	**5 Years**	**10 Years**
Conditional survival	2 years	162 (> 99)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (89)	4 (89)	259 (98)	28 (97)
	3 years	162 (100)	17 (99)	41 (100)	6 (100)	42 (93)	5 (93)	14 (90)	4 (90)	259 (98)	28 (98)
	4 years	162 (100)	17 (99)	41 (100)	6 (100)	42 (96)	5 (96)	14 (96)	4 (96)	259 (99)	28 (99)
	5 years	na	17 (99)	na	6 (100)	na	5 (100)	na	4 (100)	na	28 (> 99)

Adapted from Shields CL, Dockery PW, Mayro EL, et al. Conditional survival of uveal melanoma using the cancer genome atlas (TCGA) classification in 1001 cases. 2021. *Saudi J Ophthalmol*. [In press]. Abbreviations: na, not available

FINAL THOUGHTS

TCGA classification provides excellent prognostication in uveal melanoma and is highly predictive in estimating metastatic risk. Furthermore, encouraging data on conditional survival suggest that once a patient reaches a 5-year threshold without evident metastasis, the rate of future metastasis likely decreases. For patients in the high-risk TCGA Groups C and D, perhaps adjuvant therapies could play a role in reducing risk for metastasis. ■

1. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci*. 2003;44(11):4651-4659.
2. Shields CL, Furuta M, Thangappan A, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol*. 2009;127(8):989-998.
3. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Collaborative Ocular Melanoma Study Group. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol*. 2005;123(12):1639-1643.
4. Robertson AG, Shih J, Yau C, et al. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. *Cancer Cell*. 2017;32(2):204-220.
5. Weinstein JN, Collisson EA, Mills GB, et al. Cancer Genome Atlas Research Network: The cancer genome atlas pan-cancer analysis project. *Nat Genet*. 2013;45(10):1113-1120.
6. McLendon R, Friedman A, Bigner D, et al. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. 2008;455(7216):1061-1068.
7. Hoadley KA, Yau C, Hinoue T, et al. Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer. *Cell*. 2018;173(2):291-304.
8. Jager MJ, Brouwer NJ, Esmaeli B. The Cancer Genome Atlas Project: An integrated molecular view of uveal melanoma. *Ophthalmology*. 2018;125(8):1139-1142.
9. Vichitvejpaisal P, Dalvin LA, Mazloumi M, et al. Genetic analysis of uveal melanoma in 658 patients using the cancer genome atlas classification of uveal melanoma as A, B, C, and D. *Ophthalmology*. 2019;126(10):1445-1453.
10. Shields CL, Mayro EL, Dockery PW, et al. Ten-year outcomes of uveal melanoma based on the cancer genome atlas (TCGA) classification in 1001 Cases. *Indian J Ophthalmol*. 2021;69(7):1839-1845.
11. Merrill RM, Hunter BD. Conditional survival among cancer patients in the United States. *Oncologist*. 2010;15(8):873-882.
12. Zabor EC, Radivoyevitch T, Singh AD, et al. Conditional survival in uveal melanoma. *Ophthalmol Retina*. 2020;S2468-6530(20):30395-X.
13. Shields CL, Dockery PW, Mayro EL, et al. Conditional survival of uveal melanoma using the cancer genome atlas (TCGA) classification in 1001 cases. *Saudi J Ophthalmol*. 2021. [In press]
14. Valsecchi ME, Orloff M, Sato R, et al. Adjuvant sunitinib in high-risk patients with uveal melanoma: Comparison with institutional controls. *Ophthalmology*. 2018;125(2):210-217.
15. Middleton MR, McAlpine C, Woodcock VK, et al. A TCR/Anti-CD3 bispecific fusion protein targeting gp100, potently activated antitumor immune responses in patients with metastatic melanoma. *Clin Cancer Res*. 2020;26(22):5869-5878.
16. Bol KF, Van Den Bosch T, Schreibelt G, et al. Adjuvant dendritic cell vaccination in high-risk uveal melanoma. *Ophthalmology*. 2016;123(10):2265-2267.

ZEYNEP BAS, MD
- Fellow, Wills Eye Hospital, Philadelphia
- zeynep@shields.md
- Financial disclosure: None

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

Support provided in part by the Eye Tumor Research Foundation, Philadelphia (CLS). The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review or approval of the manuscript. Carol L. Shields, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No conflicting relationship exists for any author.

CODING ADVISOR
A Collaboration Between *Retina Today* and AMERICAN ACADEMY™ OF OPHTHALMOLOGY
Protecting Sight. Empowering Lives.

ACTION STEPS TO EFFECTIVELY MANAGE PRIOR AUTHORIZATION AND STEP-THERAPY POLICIES

The entire staff can contribute to reducing rejections.

BY JOY WOODKE, COE, OCS, OCSR

PRIOR AUTHORIZATION A preapproval process required by some insurance payers to determine coverage for a specific service. In a retina practice, these policies mostly impact intravitreal injections and surgical procedures.

STEP THERAPY A policy that requires a mandated drug therapy, typically a lower-cost drug (eg, bevacizumab) and documented failed response before initiating a preferred drug (eg, ranibizumab, aflibercept).

Successfully navigating the challenges of prior authorization (PA) and step-therapy policies can have a positive impact on your revenue cycle management. Here are four actionable steps that will lighten the burden of these policies on the retina practice.

STAY CURRENT

Payer policies vary by insurance carrier and are updated frequently. For the top insurance carriers in the practice, research the PA and step-therapy requirements for the most frequent services provided, including injection of anti-VEGF medications. Most payers require PA for the higher-cost anti-VEGF agents, but that doesn't necessarily exclude lower-cost drugs such as bevacizumab (Avastin, Genentech) or other services.

Along with these requirements, many payers have limited exceptions for requesting a retroactive PA, so identifying policies and requesting PA prior to treatment will reduce denials.

For payers with step-therapy policies, the requirements may vary. Using a mandated (generally lower-cost) drug and documenting a failed response before initiating the preferred (higher-cost) drug is the basic concept. However, it is crucial to identify each payer's definition of "failed response" based on its guidelines. It may be defined as lack of response to a 3-month regimen, visual acuity reduction, and/or certain diagnostic testing findings. Identifying the details of these policies is crucial for understanding reimbursement guidelines.

IDENTIFY PAYER NUANCES

When coding for bevacizumab intravitreal injections, the HCPCS code to use may vary by payer. Similar to the variations among the Medicare Administrative Contractors (MACs), commercial and Medicare Advantage plans may require different HCPCS codes for reporting bevacizumab for ophthalmic use.

A commercial payer may recognize J9035 for oncologic use but require J7999 for intravitreal injection. Others may deny claims unless billed with a miscellaneous HCPCS code: for example, J3490 or J3590. Payers have also published

TABLE. MEDICATION PRIOR AUTHORIZATION AND REFERRAL RESOURCE

	EYLEA (2 UNITS)		LUCENTIS (5 UNITS)		TRIESENCE		OZURDEX		AVASTIN		SPECIAL INSURANCE REQUIREMENTS
	PA	REF	PA	REF	PA	REF	PA	REF	PA	REF	
HMA COMMERCIAL	CALL		CALL		CALL		CALL		CALL		Prior authorization via phone request only
USA MA PLAN	✔		✔		✔		✔				PA not required for Avastin
BB MA PLAN	✔		✔		✔		✔				Requires step therapy
MEDICARE PART B											**confirm secondary coverage if HMO and PA/REF requirements
CARE COMMERCIAL	✔	HMO	✔	HMO	✔	HMO	✔	HMO	✔	HMO	888-222-2222 REF needed for HMO plans (from PCP only)
MEDICAID HMO	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	
HMO INSURANCE	✔	HMO	✔	HMO	✔	HMO	✔	HMO	✔	HMO	REF needed for choice or medical home plans only

✓= PA is required; HMO=HMO referral required; CALL=PA is required, call in request; purple=no PA or referral required; yellow=caution–confirm other coverage requirements.
Source: Woodke EJ. The Profitable Retina Practice: Medication Inventory Management. American Academy of Ophthalmic Executives. 2019. https://www.aao.org/Assets/e7689602-5fbd-4c77-b1b6-6e1db0009e0c/637115818701500000/medication-inventory-management-pdf.

policies that allow J9035 with a PA but do not require PA if bevacizumab is coded with C9257, which is usually coded only as facility billing. Understanding PA policies is one step, but confirming any unusual coding requirements for bevacizumab will further streamline the process.

ASSIGN A PA SPECIALIST

Designating a staff member to be the PA expert in the practice can be advantageous. This individual can be made responsible for proactively identifying new or revised payer policies and providing internal education. As payers often update policies with limited or no communication, tasking a staff member to research these changes and promptly notify all stakeholders will limit unexpected PA or claim rejections.

DEVELOP AN INTERNAL RESOURCE

Given the challenges of policies varying by payer, it can be helpful to create an internal reference guide. This document can provide quick access to PA or step-therapy guidelines for a specific service, medication, or payer (Table). Such an internal resource can also indicate when a referral is required by a health maintenance organization.

Practice management systems often provide alerts or reminders when a service is ordered for a specific insurance payer. These automated tools can prompt the user to obtain PA or review step-therapy guidelines.

There are many types of resources that can assist with the PA process. The key is that such resources should be easily accessible, effective, and constantly reviewed and updated to stay current with payer rules.

INVOLVE THE TEAM

From check-in to examination, each person involved in the patient encounter can help to ensure that the PA process is correctly completed. This requires the oversight of the PA specialist, a commitment to education with access to current quick reference guides, and adherence to the following steps.

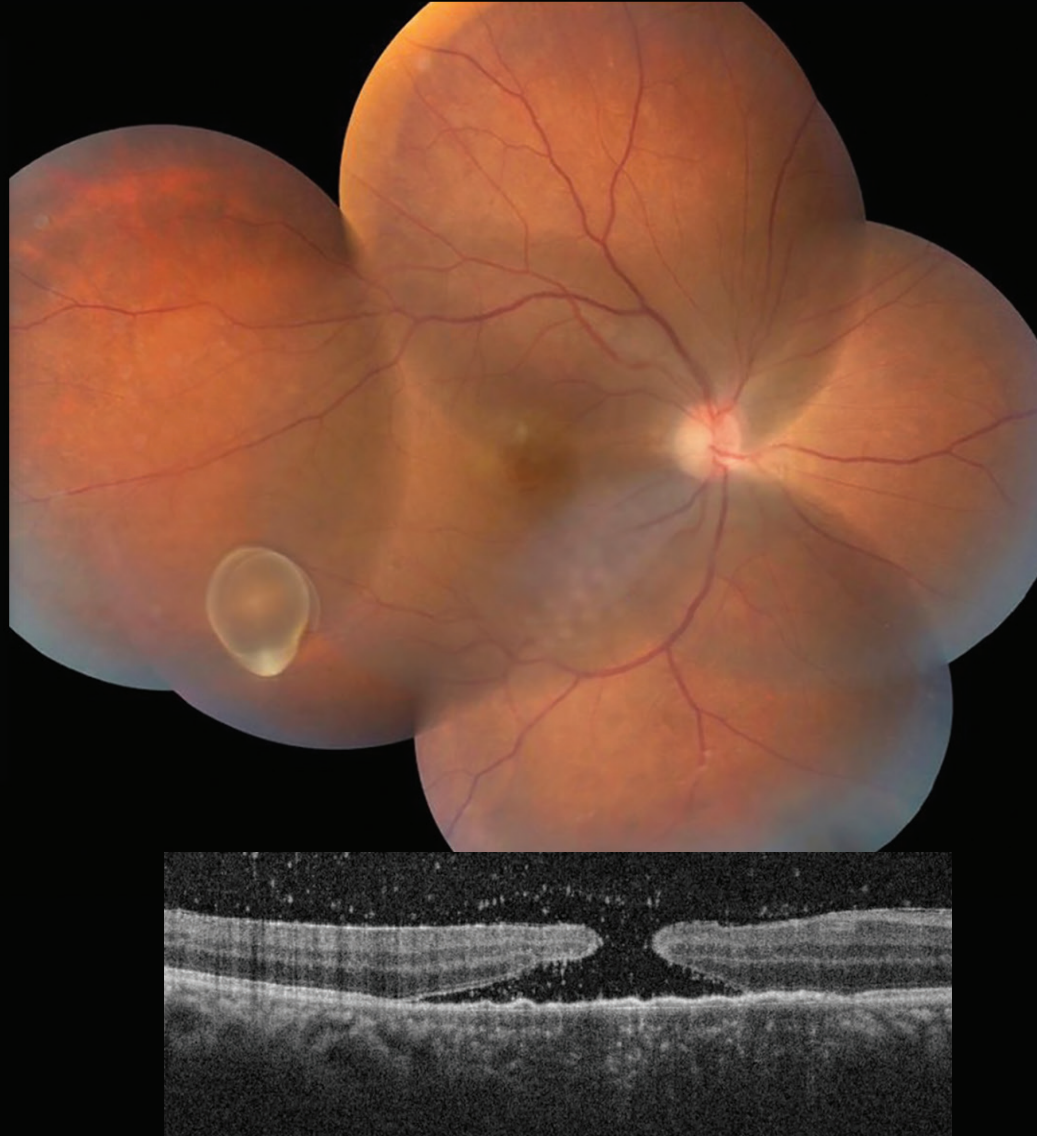
- Prior to an encounter, staff members review scheduled procedures for referral, PA, or step-therapy requirements and request as appropriate.
- During the check-in process, the staff confirms the patient's current insurance carrier and checks eligibility.
- Scribes prompt the retina specialist regarding specific payer requirements when services are ordered.
- Business office staff confirm that authorization is requested or received prior to claim submission.
- When staff members identify a change in payer policy, all internal resources are updated and all stakeholders notified.

Diligence and teamwork are essential for any process, including navigating PA requirements and payer policies. In a retina practice, this is crucial, and a commitment from the entire practice team will contribute to overall success.

For more AAO resources on PA and step therapy, including a PA checklist, visit aao.org/retinapm. ■

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

INTRAVITREAL CYSTICERCOSIS WITH FULL THICKNESS MACULAR HOLE



This rare presentation was managed with vitrectomy, membrane peeling, and excision of the cyst.

BY VISHAL AGRAWAL, MD, FRCS

A 41-year-old man presented with diminution of vision in his right eye for 3 months. VA was 20/400 OD. On fundus examination, a solitary live intravitreal cysticercus cyst was noted (Main Figure). Spectral-domain OCT showed a large full-thickness macular hole of 1,500 µm diameter with retinal pigment epithelium alterations at the macula (Inset). The anterior segment examination was unremarkable. Neuroimaging showed no involvement of the central nervous system.

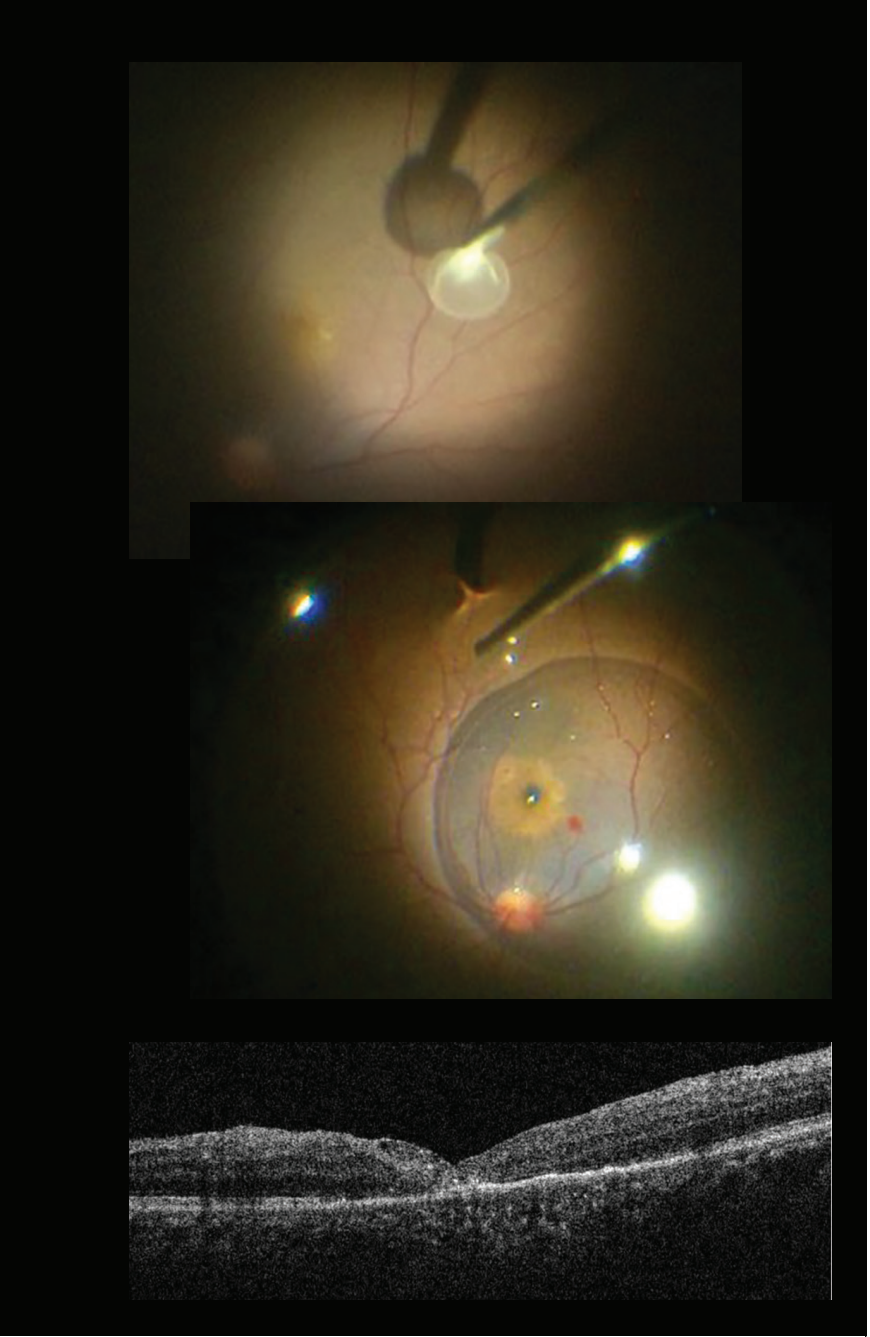
The patient underwent 23-gauge pars plana vitrectomy. Intraoperatively, the cyst was aspirated with the cutter (Top Figure, Right). To address the macular hole, inverted internal limiting membrane (ILM) peeling was performed under a bubble of perfluorocarbon liquid (PFCL; Middle Figure, Right).

Postoperatively, OCT revealed a type 1 closure of the macular hole (Bottom Figure, Right) and the absence of any inflammation. BCVA at final follow-up was 20/80 OD.

DISCUSSION

Live intravitreal cysticercus with a macular hole is a rare occurrence.[1,2] The management technique that has been described includes aspiration of the cyst in the vitreous cavity and inverted ILM peeling for the macular hole, performed under a bubble of PFCL. ILM peeling under PFCL is atraumatic and ensures excellent stability of the flap.

Intraocular cysticercosis has a good prognosis if managed early with pars plana vitrectomy. Delayed presentation or late intervention can lead to irreversible sight-threatening complications including retinal detachment, proliferative vitreoretinopathy, complicated cataract, and hypotony. Concurrent referral to neurology to rule out neurocysticercosis should be an integral part of the workup, as should advising the patient regarding proper food hygiene. ■



1. R K, Ravani RD, Kakkar P, Kumar A. Intravitreal cysticercosis with full thickness macular hole: management outcome and intraoperative optical coherence tomography features. *BMJ Case Rep*. 2017;2017:bcr-2016-218645.
2. Dhiman R, Devi S, Duraipandi K, et al. Cysticercosis of the eye. *Int J Ophthalmol*. 2017;10(8):1319-1324.

VISHAL AGRAWAL, MD, FRCS
- Professor of Ophthalmology, Sawai Man Singh Medical College, Jaipur, India
- drvishalrpc@yahoo.com
- 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)

If you have an image or images you would like to share, email Dr. Nagpal.
Note: Photos should be 400 dpi or higher and at least 10 inches wide.

INDEX OF ADVERTISERS

BVI **29**
www.bvimedical.com
Euretina **49**
www.euretina.org
EyePoint Pharmaceuticals **7, 8**
www.eyepointpharma.com
Genentech ..... **59, Cover 4**
www.genentech.com
Iveric Bio ..... **Cover 2**
www.ivericbio.com
MedOne Surgical **21**
www.medone.com
Notal Vision **5**
www.notalvision.com
Oculus **41**
www.oculussurgical.com
Quantel Medical **17**
www.quantel-medical.com

This advertiser index is published as a convenience and not as part of the advertising contract. Although great care will be taken to index correctly, no allowances will be made for errors due to spelling, incorrect page number, or failure to insert.

AARON NAGIEL, MD, PHD

What made you want to specialize in pediatric retinal disorders?

As an MD-PhD student at Cornell and Rockefeller University, I studied neural development in zebrafish and became interested in the patterning and genetics of sensory tissues. This got me interested in pediatric retina as a potential clinical specialty. It just kind of clicked in my mind that this is what I should do, especially since I enjoy working with children. As I neared completion of my PhD, I reached out to R.V. Paul Chan, MD, MSc, MBA, FACS, who was at Cornell at the time, to discuss this further. In the first 5 minutes of our meeting, he emailed Thomas C. Lee, MD, at Children's Hospital Los Angeles, to secure me an away rotation the following summer. Seven years later, I was hired by Dr. Lee to join him there on the faculty. I'm so appreciative to have had these two incredible mentors in the field.

You have an active laboratory and translational research program that is developing novel therapeutic approaches for children with diseases of the retina and vitreous. What are your goals for the next few years?

I have been fortunate enough to have received significant extramural research funding for my laboratory program, including a Mentored Clinical Scientist Research Career Development Award (K08) from the National Eye Institute and a Research to Prevent Blindness Career Development Award. I hope to capitalize on this support to identify how synaptogenesis occurs in the human outer plexiform layer, at the first synapse of the visual system. My hope is that by studying this process during development we can understand how it goes awry in retinal disease and learn how to ensure the proper restoration of synaptic connectivity following gene and cell therapies.

In 2018, you performed the first voretigene neparvovec (Luxturna, Spark) gene therapy procedure on the West Coast. What was that experience like?

There was a great deal of trepidation on my part, making sure all the logistic considerations were taken care of and ensuring that I had thought through all of the possible intraoperative scenarios. The weekend before the surgery, I went with my family to a retreat in the foothills of Ojai, California, to clear my mind and prepare. Thankfully our first patient was a pseudophakic middle-aged man with advanced disease, which relieved some of the pressure. That being said, we still offered this burly gentleman with a lumberjack beard a ride to the OR in a wagon while holding a Children's Hospital Los Angeles teddy bear!

What new technological advances do you find particularly exciting? Which advances in the pipeline are you most enthusiastic or curious about?

Dr. Nagiel having a fun day at the beach in Malibu with his family.

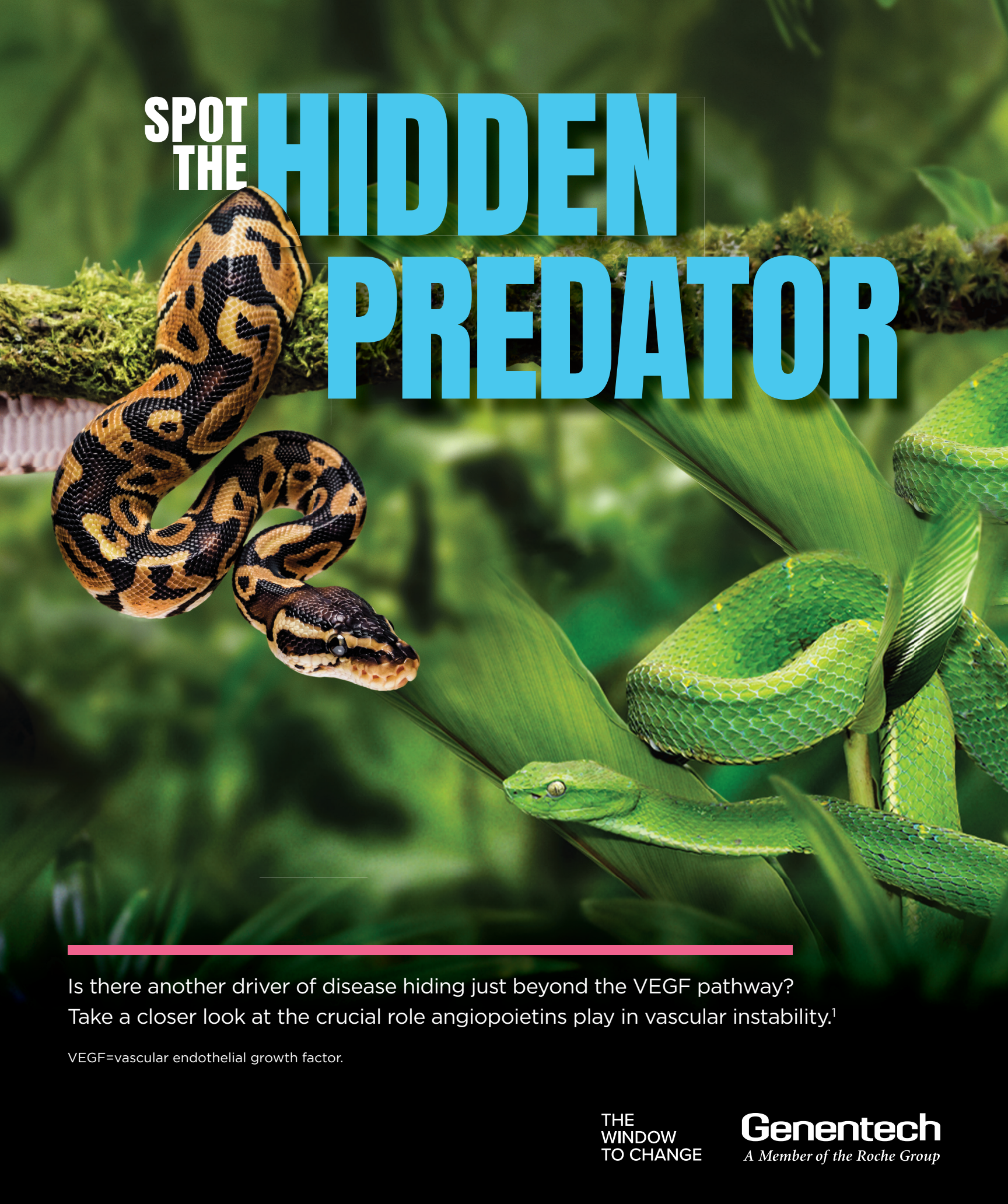
We are living in an incredible era where genetic medicines are truly putting the "personal" in personalized medicine. The pharmaceutical paradigm of designing drugs meant to treat the largest possible number of patients has been completely turned on its head. The most exciting new developments are coming from the increasing personalization of our treatment strategies. Voretigene is one example—a therapy for which only patients with mutations in the *RPE65* gene are eligible. But this is just the tip of the iceberg as novel strategies, such as CRISPR editing and exon skipping, are being implemented to address specific mutations or exons. It is humbling and exhilarating to be a retina specialist today and see how our specialty is paving the way for the rest of medicine.

What do you like to do when you aren't in the office? What are your hobbies and interests?

Going on outings and having fun at home with my wife and three daughters have always been big highlights of my life outside of work, especially during the pandemic when everything else seemed to come to a halt. I am addicted to the NY Times crossword puzzles app and have become a Peloton fanatic (Leaderboard name: Silpancho)—shout out to my fellow retina Peloton riders! ■

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, Regenxbio)

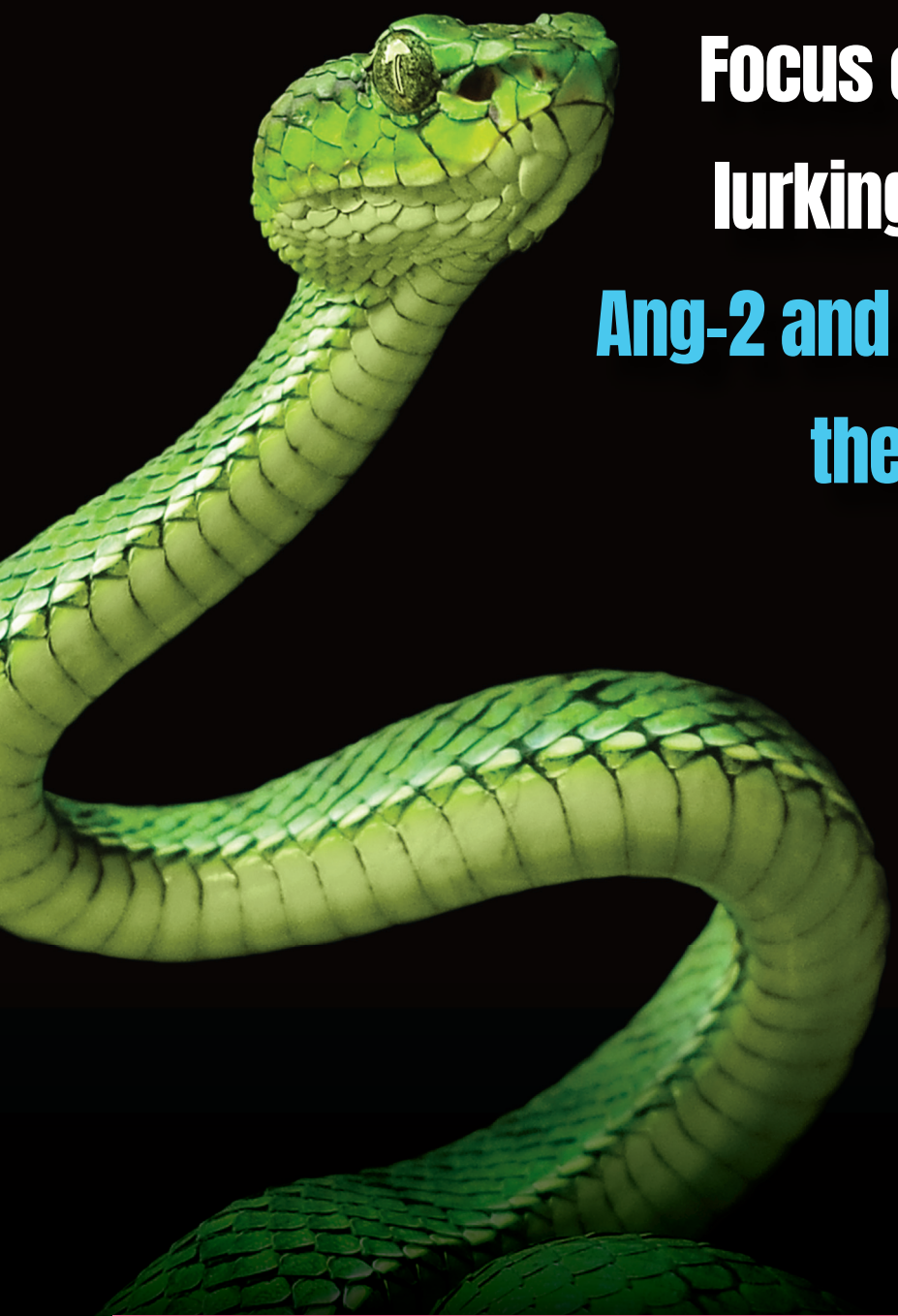


Is there another driver of disease hiding just beyond the VEGF pathway? Take a closer look at the crucial role angiopoietins play in vascular instability.[1]

VEGF=vascular endothelial growth factor.

THE WINDOW TO CHANGE

Genentech
A Member of the Roche Group



Focus on the threat that's lurking in nAMD and DME:

Ang-2 and its ability to inhibit the Ang-Tie pathway[1,2]

See the potential of Ang-2 at thehiddenpredator.com

Ang-2=angiopoietin-2; Ang-Tie=angiopoietin/Tie; DME=diabetic macular edema; nAMD=neovascular age-related macular degeneration.

References: 1. Saharinen P, et al. *Nat Rev Drug Discov.* 2017;16:635-661.
2. Fiedler U, et al. *Nat Med.* 2006;12:235-239.

THE
WINDOW
TO CHANGE

Genentech
A Member of the Roche Group