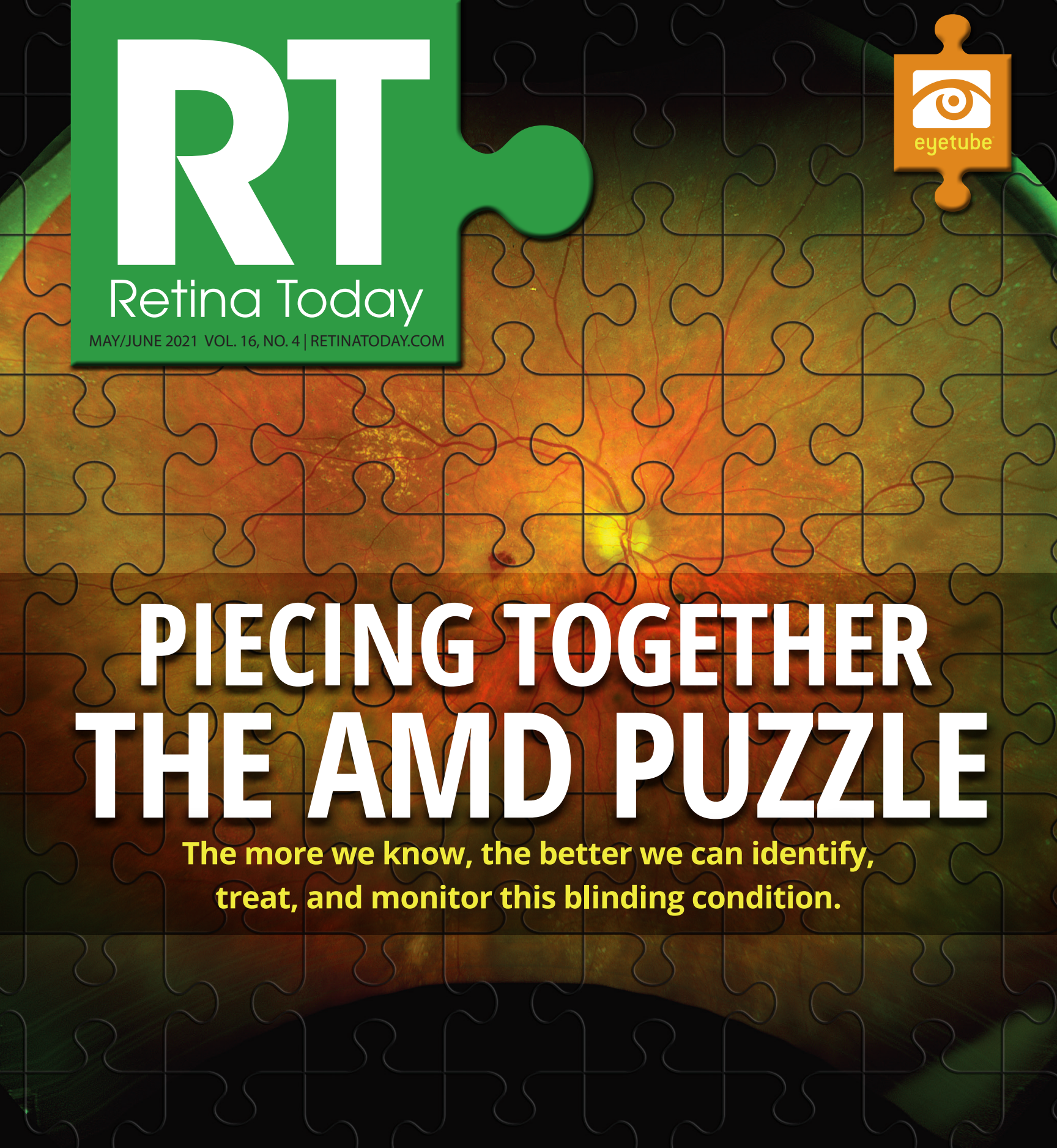
RT
Retina Today
MAY/JUNE 2021 VOL. 16, NO. 4 | RETINATODAY.COM

eyetube



PIECING TOGETHER THE AMD PUZZLE

The more we know, the better we can identify, treat, and monitor this blinding condition.

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.

A SLOW AND STEADY... BOOM?


In 1999, *Time* quoted geneticist W. French Anderson, MD, as saying, "Twenty years from now gene therapy will have revolutionized the practice of medicine. Virtually every disease will have gene therapy as one of its treatments."[1]

In that *Time* article, Dr. Anderson was touting recent advances in gene therapy for heart disease that were finally showing some promise after 8 years of work. At the time, researchers were encouraged by signs of efficacy but had yet to see a successful protocol, as a whole, for gene therapy.

Alas, we have surpassed the 20-year mark (21 to be exact) since Dr. Anderson's remarks, and we are still a far cry from achieving his vision. Gene therapy remains in its infancy for the vast majority of medical specialties, and it's an FDA-approved option for only two conditions: Leber congenital amaurosis (approved in 2017) and spinal muscular atrophy (approved in 2019).

For most retina specialists, the fact that the eye was the organ privileged with the first successful gene therapy came as no surprise, considering the eye's unique features. It is self-contained and provides easy viewing. Because of that, we've had something of a boom in ocular gene therapy research. In fact, so many novel agents are under investigation that we couldn't discuss all of them in this issue's featured article, "The New Frontier: Gene Therapy for AMD." Instead, we focused on a subset of therapeutics for this leading cause of adult blindness in the developed world.

Although the approved gene therapy for Leber congenital amaurosis is ground-breaking and certainly life-changing for appropriately treated patients, just *imagine* how many patients we could help if one of the several proposed gene therapies for AMD pans out.

But let's not get ahead of ourselves. The promise of a one-and-done treatment for AMD is alluring, but trials are in early stages, or just starting pivotal programs, and much can change as the data roll out and long-term follow-up reveals the lasting effects. (By the way, stay tuned for part 2 of the discussion, where we will dig into the specifics of gene therapies for inherited retinal diseases in the July/August issue.)

While we watch the gene therapy story slowly unfold, we have plenty to keep us on our toes in the clinic every day. We have ever-evolving imaging tools, as well as a robust armamentarium of AMD therapies, thanks to advances in anti-VEGF agents and delivery methods.

This issue, focused on AMD, touches on all of it: a new OCT classification system for macular atrophy, at-home OCT monitoring, the anti-VEGF therapy journey, pipeline drugs for nonexudative AMD, and treatment pearls for tough AMD cases.

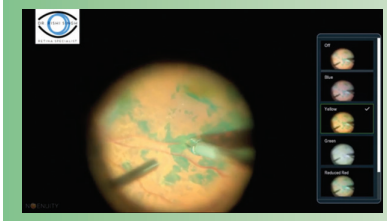
The days of sitting AMD patients down and telling them that there's nothing we can do to preserve their vision are mostly in the rear-view mirror, but there is still a great deal of work to be done. We might have to reeducate patients, *constantly*, on the importance of compliance with their treatments, but it's worth it. Because vision matters. ■

ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

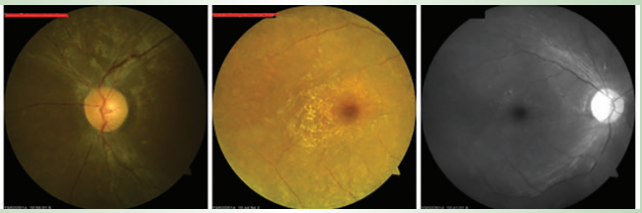
ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

1. Jaroff L. Fixing the Genes. *Time Magazine*. 1999;153(1):68-73.

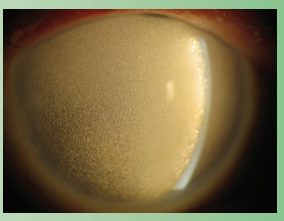
ALSO IN THIS ISSUE:



Improve membrane visualization in the OR with a 3D heads-up display, p. 10.



A case of juvenile neuronal ceroid lipofuscinosis in Ecuador, p. 14.



How to manage glaucoma after pars plana vitrectomy, p. 47.

REGENXBIO®

SEEKING TO IMPROVE LIVES THROUGH THE CURATIVE POTENTIAL OF GENE THERAPY

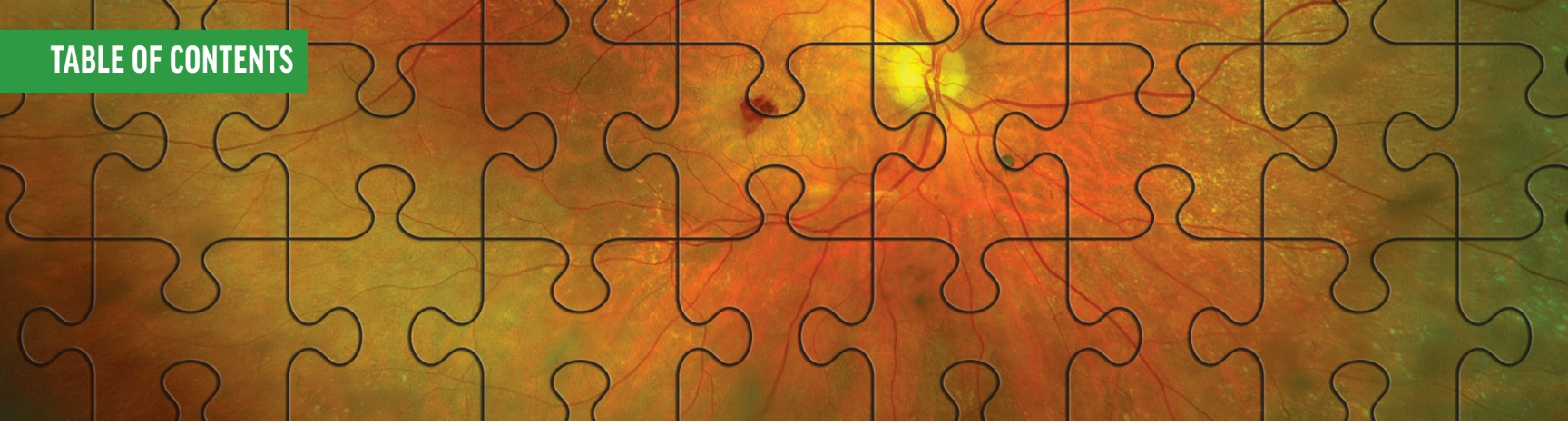
OUR COMMITMENT

REGENXBIO is committed to developing gene therapies that improve treatment options for people with serious diseases. The personal stories of patients and families help guide our work. We earn their trust through our actions and our words.

› For the latest updates on our programs, visit REGENXBIO.com

REGENXBIO.com

TABLE OF CONTENTS



Cover image credit: ©iStockphoto.com; Robert L. Avery, MD

PIECING TOGETHER THE AMD PUZZLE

DEPARTMENTS

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

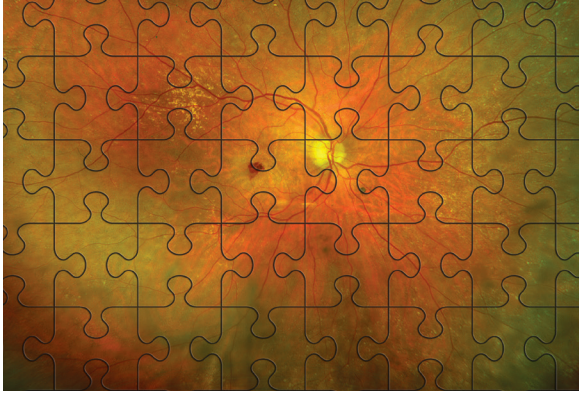
Mon-Fri, 8 AM to 6 PM EST

www.foreseehome.com/hcp

RT NEWS

MAY/JUNE 2021

VOL. 16, NO. 4 | RETINATODAY.COM



DURABLE RESULTS WITH ADVERUM'S GENE THERAPY, BUT AN UNEXPECTED SAFETY EVENT

Durable expression of aflibercept was seen 2 years after a single in-office intravitreal injection of either dose of ADVM-022 (Adverum Biotechnologies) in the OPTIC clinical trial in patients with wet AMD, according to a report at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in May. Mean BCVA and mean central retinal thickness were maintained or improved, and most patients needed no supplemental anti-VEGF injection. There was substantial reduction in annualized anti-VEGF injection frequency after ADVM-022 administration in patients who previously required frequent injections, and robust sustained aflibercept expression levels that were within therapeutic range were observed.

This positive news in the AMD trial was tempered by Adverum's announcement, just days before the ARVO meeting, of a suspected unexpected serious adverse reaction (SUSAR) of clinically relevant hypotony in one patient in the INFINITY phase 2 clinical trial of ADVM-022 in patients with diabetic macular edema (DME). This event occurred 30 weeks after randomization in one patient treated with a single intravitreal injection of the high dose of ADVM-022; the patient developed hypotony with panuveitis and loss of vision in the treated eye.

In late April, Adverum announced that, in the interest of patient safety, it was immediately unmasking the INFINITY study to better understand the event and help identify and manage any similar potential risk to other patients in the study. Additionally, Adverum said it is conducting a thorough review of data from its ADVM-022 program and plans to report findings as the analysis progresses.

"The safety of every patient who is participating in our clinical studies with our gene therapy is the utmost priority for us at Adverum," said Laurent Fischer, MD, CEO of Adverum, in a press release announcing the SUSAR. "We are fully committed to thoroughly assessing this case and ongoing monitoring of this patient and all patients treated with ADVM-022 with our investigators, data monitoring committee, scientific advisory board, and health care authorities."

As of December 2020, the INFINITY study in DME was fully enrolled and all patients had received the single intravitreal injection of ADVM-022, the company noted. All patients will continue to be evaluated regularly during the monitoring phase of the study.

For the OPTIC trial in wet AMD, interim safety and efficacy data from patients followed for a median of 88 and 68 weeks at the lower dose of 2x10^11 vg/eye (for cohorts 2 and 3, respectively) and 104 and 36 weeks at the higher dose of 6x10^11 vg/eye (for cohorts 1 and 4, respectively) were presented at ARVO. All ADVM-022–related ocular adverse events were mild (80%) to moderate (20%) with no clinical or fluorescein evidence of posterior inflammation. No vasculitis, retinitis, choroiditis, vascular occlusions, or endophthalmitis were seen in these patients.

PLASMA KALLIKREIN INHIBITOR SHOWS PROMISE FOR DME

RZ402 (Rezolute), an investigational oral plasma kallikrein inhibitor (PKI) being developed for the treatment of DME, showed positive results in a phase 1 clinical trial, the compound's developer announced in May. Single-dose oral administration of RZ402 resulted in plasma concentrations that exceeded the target pharmacologically active drug levels, demonstrating the potential for once-daily dosing and supporting advancement toward phase 2 development, according to a press release from Rezolute; next up will be a phase 1b multiple-ascending dose study.

RZ402 was generally safe and well-tolerated at all doses tested without dose-limiting toxicities, the company said.

Research has implicated the kallikrein-kinin system in the development of diabetic retinopathy and DME, said Robert B. Bhisitkul, MD, PhD, in the press release. Dr. Bhisitkul, a

professor of ophthalmology at the University of California San Francisco, is a member of Rezolute's scientific advisory board.

"Oral delivery would provide the possibility of earlier treatment intervention [for DME] and enable a patient-controlled regimen with advantages in comfort, convenience, and continuous drug levels in the retinal microvasculature," Dr. Bhisitkul said.

In the single-dose study in healthy humans, ascending doses resulted in dose-dependent increases in systemic exposure. Plasma concentrations of RZ402 exceeded the target concentration that was pharmacologically active in animal models of DME, according to the company. No serious adverse events and no imbalance of adverse events between the treatment and placebo control groups were seen in the study.

LONGER TREATMENT INTERVAL WITH BROLUCIZUMAB IN PHASE 3 DME TRIALS

The anti-VEGF agent brolucizumab 6 mg (Beovu, Novartis) met its primary endpoint in two phase 3 clinical trials, KESTREL and KITE, demonstrating noninferiority in change in BCVA from baseline versus aflibercept 2 mg (Eylea, Regeneron) at year 1 in patients with DME, according to data presented at ARVO. These were the first pivotal trials to assess an anti-VEGF agent using 6-week dosing intervals in the loading phase, suggesting that brolucizumab may allow use of fewer injections from the start of treatment, Novartis said in a May press release announcing the results.

In secondary endpoints, more patients treated with brolucizumab experienced intraretinal fluid (IRF) and subretinal fluid resolution at weeks 32 and 52 compared with aflibercept, the company said. The anti-VEGF agent also demonstrated an overall well-tolerated safety profile in the studies. A brolucizumab 3 mg arm, included only in KESTREL, did not meet the primary endpoint.

To study the potential of brolucizumab to reduce treatment burden, the study drug was given at 6-week dosing intervals during the loading phase while aflibercept was given at the standard 4-week dosing intervals, in line with its labeling. After the loading phase, more than half of patients in the brolucizumab arm (55.1% in KESTREL and 50.3% in KITE) remained on a 3-month dosing interval through year 1, using a treatment approach determined by assessment of disease activity. If disease activity was detected, brolucizumab patients were switched to a 2-month interval through the end of the trial. All aflibercept patients were on a 2-month interval after the loading phase.

Novartis said it plans to submit these 1-year data from KESTREL and KITE to global health authorities with the goal of bringing brolucizumab to market for the treatment of DME. The company said it anticipates announcing 2-year results from the two studies later in 2021.

LIGHT TREATMENT SHOWED BENEFIT IN DME

The Valeda Light Delivery System (LumiThera) photobiomodulation (PBM) treatment demonstrated improvements in clinical and anatomic outcomes in an ongoing safety and efficacy study in patients with central DME, according to a presentation at ARVO.

After the treatment, the presence of IRF overall was reduced from 90% to 70%, and the presence of IRF in the central 1 mm was reduced from 70% to 57%, presenter Hakan Kaymak, MD, said. Central retinal thickness was significantly reduced, from 294 ± 51 µm at baseline to 286 ± 42 µm.

Nineteen patients (30 eyes) with good visual acuity and DME were treated with one series of nine PBM treatments, given approximately three times a week for 3 to 4 weeks. After treatment, Diabetic Retinopathy Severity Scores showed a 1-step improvement in 17% of eyes and remained stable in 83%. More than 60% of patients noted a continuation of their subjective improvement and decreased disease influence on their daily life at 4 months after treatment.

There was no change in the other morphologic efficacy and safety parameters including epiretinal membrane, disorganization of the inner retinal layers, and integrity of the outer retina during the follow-up period.

BIOMARKER IDENTIFIED FOR PHASE 3 STUDY IN RETINITIS PIGMENTOSA

Central foveal thickness (CFT), as measured by spectral-domain OCT, can serve as an anatomic marker for response to jCell (jCyte), a regenerative cell therapy being developed for treatment of retinitis pigmentosa (RP), according to a presentation at the ARVO meeting. This biomarker will be an important inclusion criteria for a planned phase 3 pivotal study, jCyte said in a press release.

In patients who have received the high-dose jCell treatment of 6 million cells, a correlation was seen between outcomes and OCT baseline parameters, specifically the mid-subfield mean ellipsoidal zone (EZ) thickness and mean CFT. EZ recession and the thinning of the outer EZ have been identified as potential structural surrogates for RP severity.

"The identification of these important structural predictors of response aligns scientifically with the RP patient population expected to respond to jCell treatment based upon its paracrine mechanism of action," said Sunil Srivastava, MD, of the Cleveland Clinic Cole Eye Institute, who presented the results at ARVO. "These results are very encouraging as we know that jCell releases an array of well-established neurotrophic factors that have been shown to support photoreceptor function and survival in key preclinical models of RP and other retinal degenerative disorders when administered early in the disease process, prior to the significant loss of key retinal cell layers." ■

IMPROVING MEMBRANE VISUALIZATION IN THE OR

Adjusting parameters on 3D heads-up display systems can enhance the effect of dyes.

BY ALLINE G.R. MELO, MD; THAIS F. CONTI, MD; AND RISHI P. SINGH, MD

In traditional vitreoretinal procedures, the surgeon operates looking through the binoculars of a standard operating microscope (SOM). Recent technological advances now allow surgeons to view procedures with a 3D heads-up display (HUD), such as that provided by the Ngenuity 3D Visualization System (Alcon). Another system, Artevo (Carl Zeiss Meditec), came to market last year.

Several studies highlight the advantages of a 3D HUD over a SOM during retina surgery, including enhanced stereopsis, wider depth of field, improved ergonomics, increased magnification with a larger field of view, and decreased endoillumination requirements.[1,2]

THE (NOT SO) BRIGHT SIDE

In a prospective study by Talcott et al,[2] patients were randomly assigned to undergo surgery using a 3D HUD surgical platform or a SOM. The study authors found that the minimum required endoillumination was significantly lower with the 3D HUD (mean 22.70 ± 15.10% standard deviation) compared with the SOM (mean 39.06 ± 2.72%; $P < .001$) during macular surgery.[2]

The ability to reduce illumination during vitrectomy is a significant advantage because a macula exposed to high-intensity light at close proximity is susceptible to thermal and photochemical damage. Macular phototoxicity has been correlated with increased light exposure time and intensity, especially with short wavelength and UV light rays.[3] In an animal model, light-induced retinal damage was observed from a stationary endoilluminator at a distance of 2 mm from the retinal surface after 10 minutes of exposure. In a human study, 1 hour of exposure to the 150-W tungsten-halogen bulb of an operating microscope caused significant retinopathy.[4]

Reducing the power of illumination is possibe during 3D HUD surgery. Adam et al found that they could perform a vitrectomy with endoillumination reduced to 10% using 3D HUD, whereas most surgeons operate with the endoilluminator set to 40% when using a SOM.[5]

Another advantage of the Ngenuity system is its ability to apply digital filters, for example to enhance vitreous visibility or identification of internal limiting membrane (ILM) tissue. Adjustment of the color gains can augment contrast for particular situations. Altering the image with a red filter enhances visualization of ICG stain, and adding a yellow-orange filter enhances the faint staining of brilliant blue G stain. Reducing the red gain minimizes the red reflex, making the image look blue and thereby enhancing visualization of the vitreous.[1,3]

One of the most innovative features of the 3D HUD software is the ability to adjust the image's white balance and color parameters intraoperatively in real time.[6]

Unfortunately, no studies have defined the best parameters for 3D HUD, and only anecdotal experience can determine individual user and operating settings.

With colleagues at the Cole Eye Institute and the Reference Hospital in Ophthalmology in São Luis, Maranhão, Brazil, we performed a study to explore parameters that can be used to improve the visualization of epiretinal membrane (ERM) and the ILM using a 3D HUD during 25-gauge pars plana vitrectomy (PPV).[7]

STUDY DESIGN

In this observational survey-based study, we evaluated the preferred practice among surgeons using the Constellation Vision System (Alcon) and the Ngenuity. We identified 11 optical parameter profiles (OPPs) with differing brightness, contrast, gamma, hue, and saturation.[7] Brightness refers to the absolute value of color (tone)

lightness or darkness. Contrast describes the differential between light and dark areas of an image. Gamma is a parameter used to adjust the mid tones of the tonal scale, optimizing the contrast and brightness of those tones. Hue refers to the attribute of visible light as it is differentiated from or similar to the primary colors of red, green, and blue. Saturation defines the brilliance and intensity of a color.

Profile 1 represented the standard parameter setting provided out of the box from the manufacturer. For each of the other 10 OPPs, one parameter was changed while all other parameters were held constant with the values of profile 1 (Figure 1).

We video-recorded the images created by each OPP before and after staining the macular surface with ICG.

A questionnaire was used to evaluate each of the OPPs and the overall satisfaction of the 14 graders who assessed the images. After watching the video, each grader was asked to provide a grade on a scale from 1 to 7 for each OPP, with 1 being the worst and 7 the best. After grading each OPP, all graders answered four questions regarding their overall impressions:

- Could this OPP improve the visualization of the ERM before dye application?
- Does this OPP enhance ICG dye for the visualization of the ILM?
- Could this OPP replace ICG dye for the visualization of the ILM?
- Given the option, would you choose any of these OPPs for your surgeries?

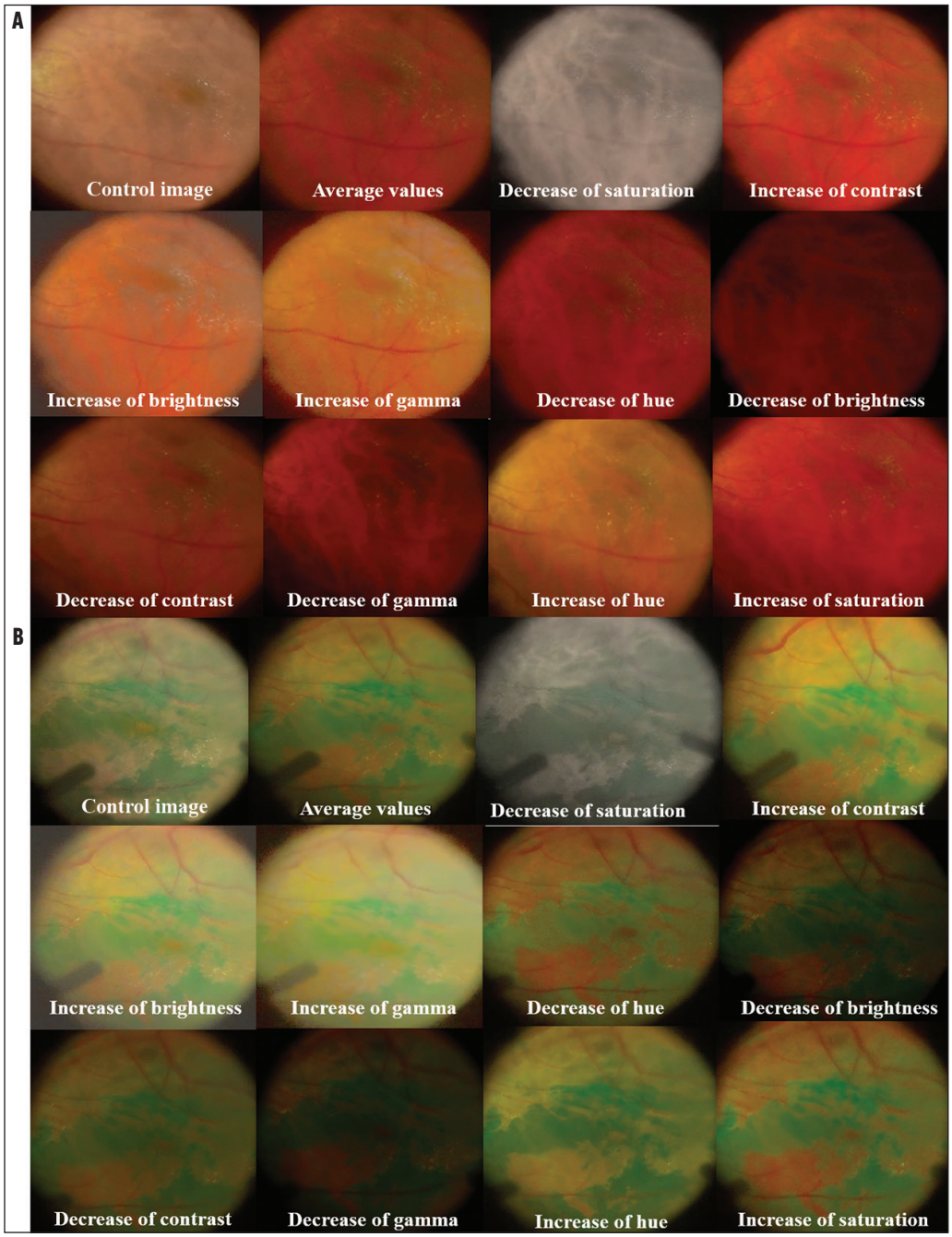


Figure 1. Intraoperative photographs of each OPP during heads-up surgery before (A) and after (B) use of ICG dye.

FINDINGS

Based on the graders' responses, higher values of hue and contrast correlated with better visualization of the ERM before dye application and better visualization of the ILM after ICG dye application. Before ICG dye, the average grade for increase in hue was 5.2 ($P < .001$) and for increase of contrast was 4.5 ($P < .001$). After ICG dye, the best average grades were for increase of hue (4.9, $P < .001$) and increase of saturation (4.7, $P < .001$).

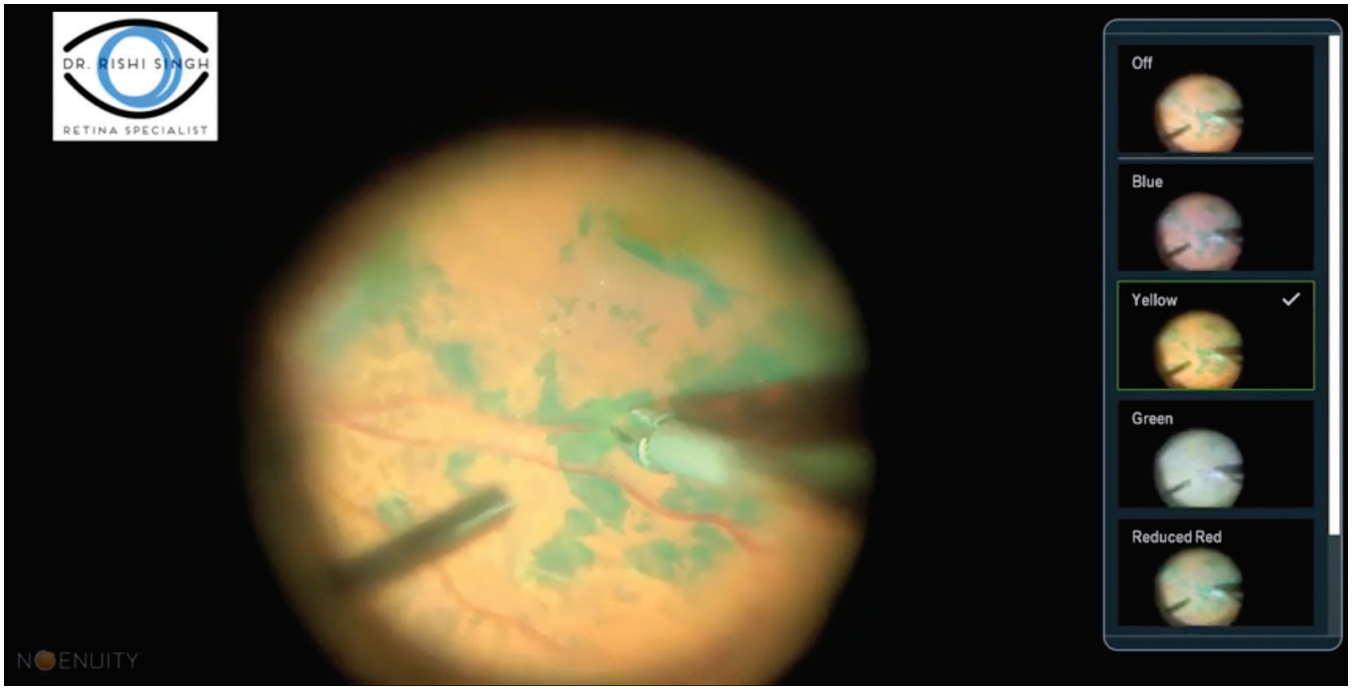


Figure 2. Enhancement in version 1.4 of the software will allow real-time color channel previews.

In assessing their overall impression, the graders agreed that the OPPs could enhance the visualization of the ERM and ILM during surgery. However, 71% of the graders stated that OPPs could not be used to replace ICG dye.

FINAL THOUGHTS

Our study demonstrated that the use of certain filters can improve the visualization of specific retinal structures such as the ILM and the ERM during PPV. Still, the technology cannot replace established surgical steps such as the use of ICG dye. Although there was no agreement among participants on an overall best parameter, feedback from the graders suggested that an increase of hue before and after ICG dye should be further explored to improve ILM and ERM visualization.

Further facilitating the use of these color channels, the most recent software upgrade (version 1.4) has improved the user's ability to change color parameters in real time (Figure 2). With this upgrade, users can preview the color channels to determine which is best during surgery. In addition, this latest software version expands the number of channels and image temperature controls for users to further refine the surgical parameters.

The use of specific OPPs to improve visualization of certain structures is a novel approach, the utility of which will be heavily dependent on surgeon preference. Investigation into the full potential of 3D HUD platforms is still in its early stages. Studies such as ours will be instrumental in improving the utility of these platforms in the OR. ■

1. Charles S. Getting specific about 3-D visualization. *Retina Today*. 2017;12(8):48-49.
2. Talcott KE, Adam MK, Sioufi K, et al. Comparison of a three-dimensional heads-up display surgical platform with a standard operating microscope for macular surgery. *Ophthalmol Retina*. 2018;3(3):244-251.
3. Asani B, Siedlecki J, Schworm B, et al. 3D heads-up display vs. standard operating microscope vitrectomy for rhegmatogenous retinal detachment. *Front Med (Lausanne)*. 2020;7:615515.
4. Kuhn F, Morris R, Massey M. Photic retinal injury from endoillumination during vitrectomy. *Am J Ophthalmol*. 1991;111(1):42-46.
5. Adam MK, Thornton S, Regillo CD, Park C, Ho AC, Hsu J. Minimal endoillumination levels and display luminous emittance during three-dimensional heads-up vitreoretinal surgery. *Retina*. 2017;37(9):1746-1749.
6. Romano MR, Cennamo G, Comune C, et al. Evaluation of 3D heads-up vitrectomy: Outcomes of psychometric skills testing and surgeon satisfaction. *Eye (Lond)*. 2018;32(6):1093-1098.
7. Melo AGR, Conti TF, Hom GL, et al. Optimizing visualization of membranes in macular surgery with heads-up display. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51(10):584-587.

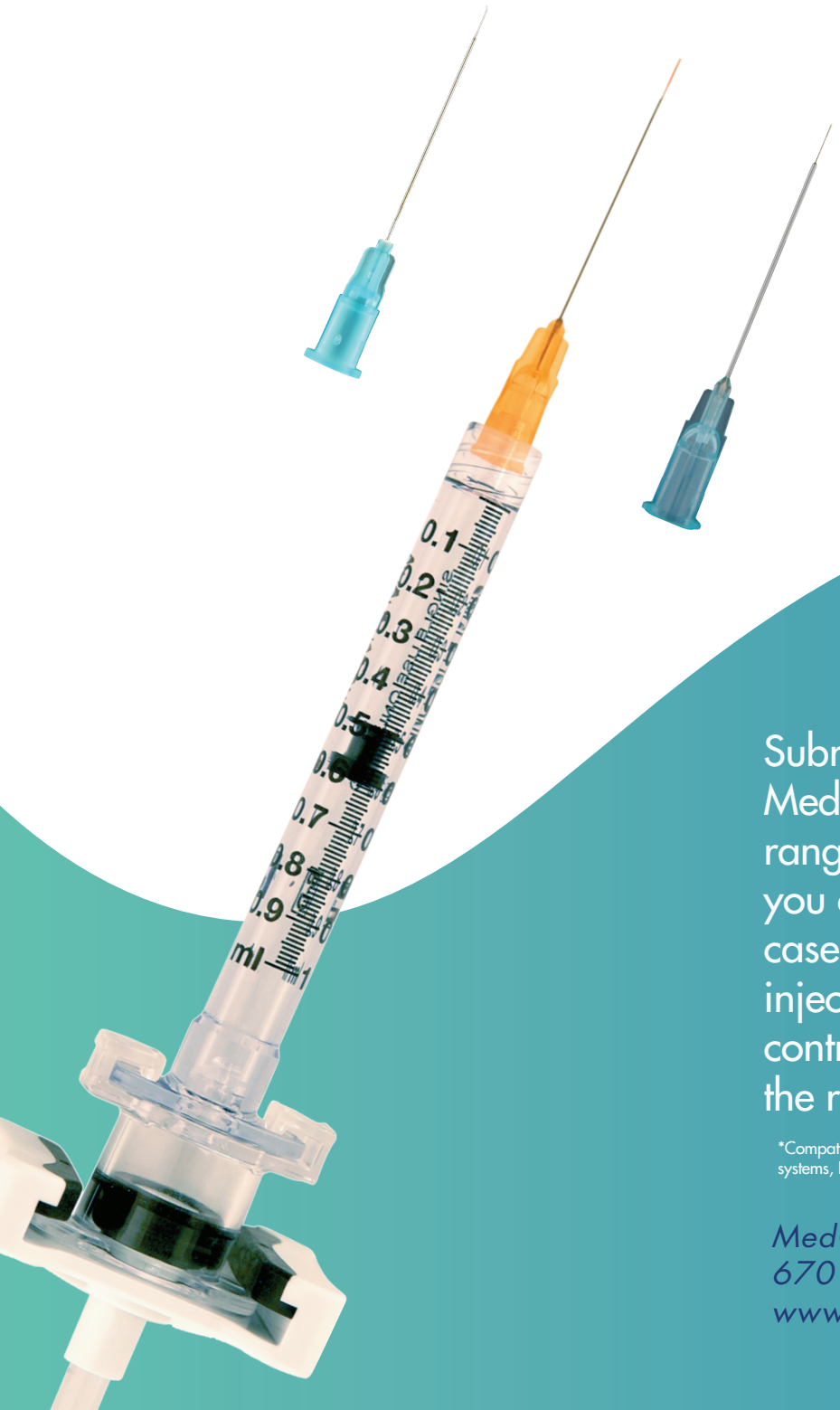
THAIS F. CONTI, MD
- Research Fellow, Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland
- thaisfconti@gmail.com
- Financial disclosure: None

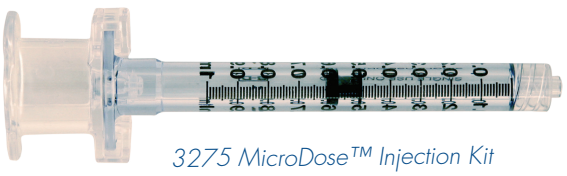
ALLINE G.R. MELO, MD
- Physician, Reference Hospital in Ophthalmology, São Luis, Maranhão, Brazil
- alline_melo@yahoo.com.br
- Financial disclosure: None

RISHI P. SINGH, MD
- Staff Physician, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland
- Associate Professor of Ophthalmology, Lerner College of Medicine, Case Western Reserve University, Cleveland
- drrishisingh@gmail.com
- Financial disclosure: Consultant (Alcon, Novartis, Genentech, Regeneron, Bausch+Lomb, Zeiss, Gyroscope); Sponsored Research (Apellis, Ocular Therapeutix, Aerie, Graybug)

PROVIDING SOLUTIONS FOR SUBRETINAL INJECTIONS

Control + Precision with our MicroDose™ Injection Kit and Subretinal Cannulas





3275 MicroDose™ Injection Kit

Kit includes preassembled adapter and syringe

MedOne®

Subretinal injections are challenging. Let MedOne help make it easier with our wide range of subretinal injection cannulas so you can select the one that is best for each case. Connect that with our MicroDose injection Kit to give you precision and total control over the injection process. Having the right tools can make the job easier.

*Compatible with the Alcon Constellation®, Bausch & Lomb Stellaris® and DORC Eva® systems, Developed in cooperation with David M. Brown, MD, Houston, TX.

MedOne Surgical, Inc. • TEL: 941.359.3129
670 Tallevast Road, Sarasota, FL 34243 USA
www.MedOne.com • MedOne@MedOne.com

CLASSICAL PRESENTATION, UNLIKELY GEOGRAPHICAL LOCATION

This case of juvenile neuronal ceroid lipofuscinosis may be the first reported in Ecuador.

BY JUAN PABLO MURILLO-ZAMBRANO, MD; MARÍA F. OSORIO, MD; JORGE MURILLO ACUÑA, MD; SIMONE FINZI, MD, PHD; AND MARC SAFRAN, MD

Juvenile neuronal ceroid lipofuscinosis (JNCL), or Batten disease, is the most common neuronal ceroid lipofuscinosis and is characterized by lysosomal accumulation of autofluorescent storage material in most tissues.[1] JNCL is an autosomal recessive alteration of the *CLN3* gene.[1]

JNCL typically presents with visual loss between 4 and 8 years of age, followed by learning impairments and motor disorders with parkinsonism by age 15 years; other clinical symptoms include seizures, ataxia, dementia, and mental retardation.[2,3] Death occurs between ages 20 and 25 years.[1]

To the best of our knowledge, this is the first case report of JNCL with a *c.1001 G-A* (*Arg334His*) variant in South America, and the first JNCL case reported in Ecuador.

CASE REPORT

A 12-year-old boy was referred to our clinic in Ecuador with functional visual loss of unknown etiology. At 7 years of age, he had experienced visual acuity decline to 20/200 OD and 20/400 OS, which rapidly evolved over 19 months to light perception OD and no light perception OS.

At 8 years, a fundoscopic examination revealed pallor of the patient's optic disc, vascular attenuation, and a diffuse grainy appearance of the retinal pigment in the periphery in both eyes (Figure 1). Electroretinography (ERG) revealed bilateral low amplitude for waves A, B, and C under scotopic conditions, suggestive of severe pigmentary retinopathy.

At presentation to our clinic at age 12, the patient's visual acuity remained the same. Neurologic examination was abnormal, with the patient displaying roving eye movements, ataxia, poor speech, and impaired cognitive ability. He had met developmental milestones prior to the presentation of symptoms, but had since experienced cognitive regression.

MRI showed the presence of a mega cisterna magna (Figure 2). Family history revealed that the patient's younger sister had experienced visual decline 1 year prior, and another boy with a similar last name in the same village had also presented with similar symptoms.

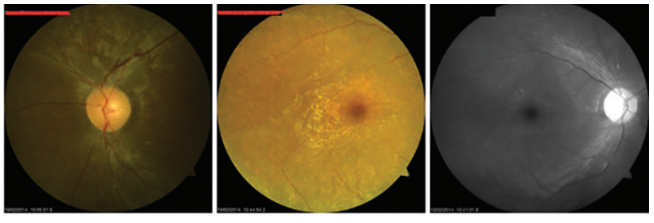


Figure 1. Fundoscopy at presentation showed pallor of the optic disc, vascular attenuation, and a diffuse grainy appearance of pigment in the retinal periphery.

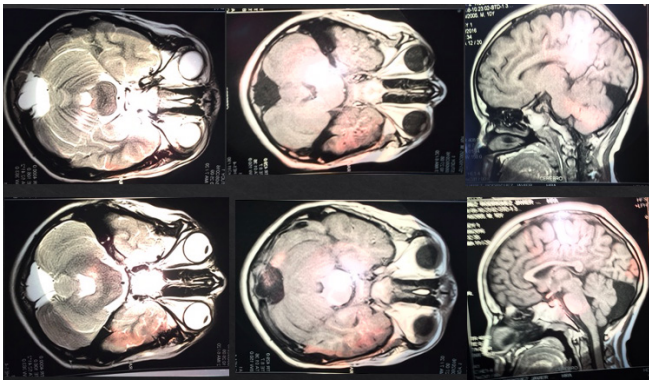


Figure 2. Head MRI showed the presence of mega cisterna magna.

Follow-up fundus examination revealed circular bands of shades of pink and orange in the retina resembling bull's eye maculopathy, mild bone spicule pigmentation in the retinal periphery, and nerve fiber layer atrophy (Figure 3). Genetic testing revealed a mutation on the *CLN3* gene with the variant *Arg334His*, consistent with JNCL.

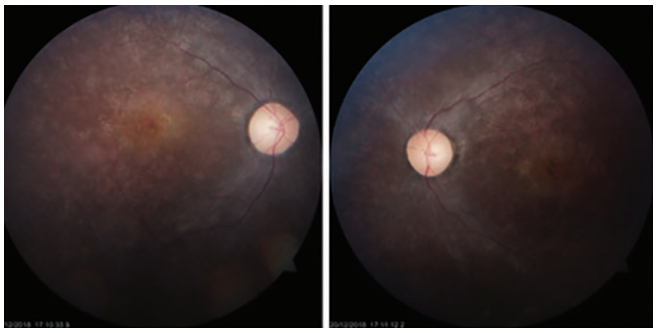


Figure 3. Follow-up fundoscopy after 4 years revealed circular bands of shades of pink and orange in the retina (resembling bull's eye maculopathy), mild bone spicule pigmentation in the retinal periphery, and nerve fiber layer atrophy.

DISCUSSION

JNCL is one of the most common pediatric neurodegenerative disorders. It is caused by mutations in the *CLN3* gene, which encodes a novel 438 amino acid protein located in lysosomes, Golgi bodies, mitochondria, and lipid rafts; the protein's function remains unknown.[1]

The classical presentation of JNCL begins with insidious but rapidly progressive vision loss between ages 4 and 7 years due to the loss of neurons from all retinal layers.[2,3] JNCL progresses to cognitive decline, leading to dementia, behavioral impairment, sleep disturbance, hallucinations or delusions, speech impairment, and parkinsonism; generalized tonic-clonic seizures appear around 10 years of age.[1] JNCL leads to death in the third decade of life.

Our patient's fundus findings included all of the classical JNCL retinal signs: early macular alteration (ie, a bull's eye pattern with a brownish color of the macula), narrowing of the vessels, peripheral bone spicules, and a pale optic disc.[2-5]

In patients with retinal degenerations, ERG provides a better understanding of the visual impact compared with visual acuity.[2] In our patient, ERG showed low A and B wave amplitudes in scotopic and photopic conditions, demonstrating a rod–cone dystrophy, a classical finding in JNCL,[2,3] especially in patients with early onset disease.[4,5]

Neurologic examinations are usually abnormal, as 75% of JNCL patients develop disorders such as cognitive impairment, change in mood or behavior, and gait disturbances.[3,5] The main neuroimaging findings are cerebral atrophy, cerebellar atrophy, and periventricular and thalamic signal changes.[6] In this patient, MRI showed the presence of a cerebellar cyst.

In Latin America, there have been only a few reports of JNCL.[7] In Brazil, Valadares et al[4] reported JNCL phenotypes in 10 affected children of one family. Visual loss was the first symptom in nine of 10 affected children, and almost all of them reported classic signs of JNCL (dementia, behavior alteration, and parkinsonism); seizures started between 8 and 12 years of age in eight of nine patients.[7]

There are a total 59 associated *CLN3* mutations: 12 missense, 13 nonsense, 16 splice-site affecting, 11 deletions, six insertions, and one mutation affecting the first methionine.[8] In our patient, genetic testing revealed a homozygous missense mutation on *CLN3* with the variant *Arg334His* on exon 13. Munroe et al described this variant in a patient with a classical clinical presentation. Other missense mutations that also affect residue 330 or 334 present with classical JNCL as well, suggesting a critical role for normal function of the CLN3 protein.[9]

The homozygous *Arg334His* mutation has been reported in Canada, Finland, the United Kingdom, Germany, Spain, and the United States;[10] but, to the best of our knowledge, this is the first case report of this variant in Latin America. ■

1. Ostergaard JR. Juvenile neuronal ceroid lipofuscinosis (Batten disease): current insights. *Degener Neurol Neuromuscul Dis*. 2016;6:73-83.
2. Eksandh LB, Ponjavic VB, Munroe PB, et al. Full-field ERG in patients with Batten/Spielmeyer-Vogt disease caused by mutations in the CLN3 gene. *Ophthalmic Genet*. 2000;21(2):69-77.
3. Bohra LI, Weizer JS, Lee AG, Lewis RA. Vision loss as the presenting sign in juvenile neuronal ceroid lipofuscinosis. *J Neuroophthalmol*. 2000;20(2):111-115.
4. Valadares ER, Pizarro MX, Oliveira LR, et al. Juvenile neuronal ceroid-lipofuscinosis: clinical and molecular investigation in a large family in Brazil. *Arq Neuropsiquiatr*. 2011;69(1):13-18.
5. Ku CA, Hull S, Arno G, et al. Detailed clinical phenotype and molecular genetic findings in CLN3-associated isolated retinal degeneration. *JAMA Ophthalmol*. 2017;135(7):749-760.
6. Wright GA, Georgiou M, Robson AG, et al. Juvenile Batten disease (CLN3): detailed ocular phenotype, novel observations, delayed diagnosis, masquerades, and prospects for therapy. *Ophthalmol Retina*. 2020;4(4):433-445.
7. Autti T, Raininko R, Vanhanen S, Santavuori P. MRI of neuronal ceroid lipofuscinosis. I. Cranial MRI of 30 patients with juvenile neuronal ceroid lipofuscinosis. *Neuroradiology*. 1996;38(5):476-482.
8. Kousi M, Lehesjoki A-E, Mole SE. Update of the mutation spectrum and clinical correlations of over 360 mutations in eight genes that underlie the neuronal ceroid lipofuscinoses. *Hum Mutat*. 2012;33(1):42-63.
9. Munroe PB, Mitchison HM, O'Rawe AM, et al. Spectrum of mutations in the Batten disease gene, CLN3. *Am J Hum Genet*. 1997;61(2):310-316.
10. Gardner E, Mole S. NCL Resource - A gateway for Batten disease. Accessed March 31, 2021. www.ucl.ac.uk/ncl-disease

JORGE MURILLO ACUÑA, MD
- Director, Centro Oftalmológico Murillo Visión, Guayaquil, Ecuador
- Financial disclosure: None

SIMONE FINZI, MD, PHD
- Director, Ocular Genetics Service, Department of Ophthalmology, University of São Paulo, São Paulo, Brazil
- Financial disclosure: None

JUAN PABLO MURILLO-ZAMBRANO, MD
- Researcher, School of Medicine, Universidad Espíritu Santo-Ecuador, Guayaquil, Ecuador
- Medical Assistant, Centro Oftalmológico Murillo Visión, Guayaquil, Ecuador
- Financial disclosure: None

MARÍA F. OSORIO, MD
- Researcher, School of Medicine, Universidad Espíritu Santo-Ecuador, Guayaquil, Ecuador
- maferosorio@uees.edu.ec
- Financial disclosure: None

MARC SAFRAN, MD
- Director, Clay Eye Center, Liverpool, New York
- Financial disclosure: None

The authors kindly acknowledge the patient's family, the personnel of Clay Eye Center, the Instituto Oftalmológico Matamoros at Guayaquil, and, especially, Ivan Matamoros, MD, and Nelson Matamoros, MD.

Beovu®
(brolucizumab-dbll)
Injection

Dosage & Administration: BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first 3 doses, followed by 1 dose of 6 mg (0.05 mL) every 8-12 weeks.

INDICATIONS AND USAGE

BEOVU® (brolucizumab-dbll) injection is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

BEOVU is contraindicated in patients with ocular or periocular infections, active intraocular inflammation or known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; IRF=intraretinal fluid; Q8=treatment every 8 weeks; Q12=treatment every 12 weeks; SRF=subretinal fluid.

Contact your local Novartis Sales Specialist or learn more at **BEOVUhcp.com**

THIS WAY TO
BEOVU DATA

For patients with wet AMD[1]

THEIR VISION IS A WORK OF ART

In 2 head-to-head trials vs aflibercept, BEOVU[1,2]:

- **Achieved** similar mean change in BCVA at Week 48[1]*
- **Started** eligible patients on Q12 immediately after loading, and **maintained** over half at Week 48 (56% and 51%)[1,2†]
- **Demonstrated** greater CST reductions and fewer patients with IRF and/or SRF as early as Week 16, and at Week 48[2‡]

In HAWK, superior CST reductions and reductions in the percentage of patients with IRF and/or SRF were achieved at Week 16 and Week 48. In HARRIER, *P* values are nominal and not adjusted for multiplicity.[2] Clinical significance has not been established. No conclusions of efficacy may be drawn.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachment

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of BEOVU. Patients should be instructed to report any change in vision without delay.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

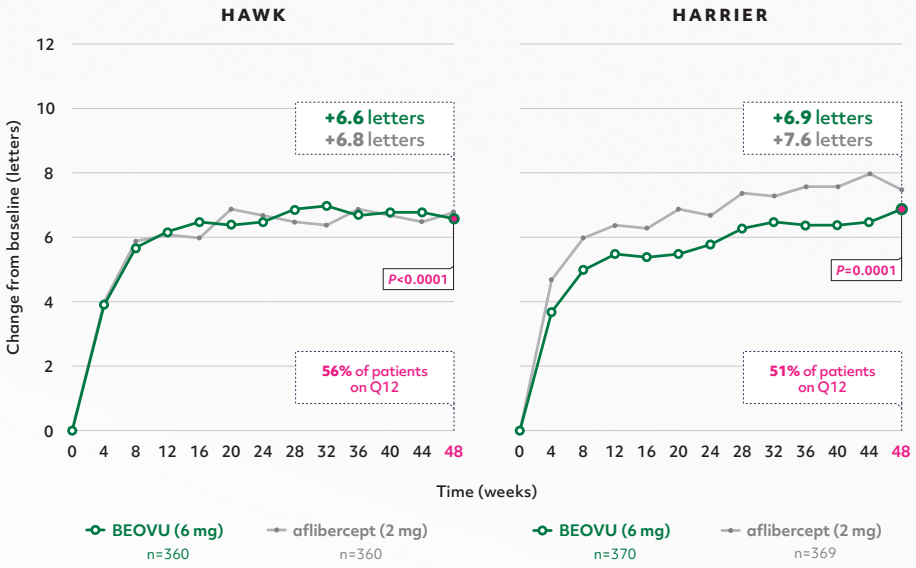
*The primary endpoint was to demonstrate efficacy in mean change in BCVA from baseline at Week 48, measured by ETDRS letters. BEOVU (Q8/Q12) demonstrated noninferiority in BCVA to aflibercept 2 mg (fixed Q8).[1]

†In HAWK and HARRIER, respectively. All remaining patients were on Q8. Patients on BEOVU could be adjusted from Q12 to Q8 at any disease activity assessment.[1,2]

‡CST reductions in patients on BEOVU vs aflibercept at Week 16 in HAWK (*P*=0.0008): -161.4 µm vs -133.6 µm; Week 48 (*P*=0.0012): -172.8 µm vs -143.7 µm. CST reductions in patients on BEOVU vs aflibercept at Week 16 in HARRIER (*P*<0.0001): -174.4 µm vs -134.2 µm; Week 48 (*P*<0.0001): -193.8 µm vs -143.9 µm. Percentage of patients with IRF and/or SRF on BEOVU vs aflibercept at Week 16 in HAWK (*P*<0.0001): 34% vs 52%; Week 48 (*P*=0.0001): 31% vs 45%. Percentage of patients with IRF and/or SRF on BEOVU vs aflibercept at Week 16 in HARRIER (*P*<0.0001): 29% vs 45%; Week 48 (*P*<0.0001): 26% vs 44%.[2-4]

Visual gains achieved with BEOVU were similar to aflibercept[1,2]

Primary endpoint: Mean change in BCVA with BEOVU vs aflibercept from baseline to Week 48[1,3,4]



The primary endpoint was to demonstrate efficacy in mean change in BCVA from baseline at Week 48, measured by ETDRS letters. Both studies confirmed the hypothesis of noninferiority at Week 48 with a margin of 4.0 letters.[1,2]

RESULTS SEEN WITH

over half of patients on Q12 at Week 48 (56% and 51%)[1]

Study design: The safety and efficacy of BEOVU were assessed in 2 randomized, multicenter, double-masked, active-controlled, 2-year, Phase III studies in patients with wet AMD (N=1459). The primary endpoint demonstrated noninferiority in mean change in BCVA from baseline to Week 48 vs aflibercept as measured by ETDRS letters. Patients were randomized to receive either BEOVU 6 mg or aflibercept 2 mg (Q8 per label). Disease Activity Assessments (DAAs) were conducted throughout the trial at prespecified intervals. After 3 initial monthly doses, treating physicians decided whether to treat each patient on a Q8 or Q12 interval guided by visual and anatomical measures of disease activity, although the utility of these measures has not been established. Patients with disease activity at Week 16 or at any DAA could be adjusted to Q8 for the remainder of the study.[1,2]

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEOVU. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

ADVERSE REACTIONS

Serious adverse reactions including endophthalmitis, retinal detachment, retinal vasculitis and/or retinal vascular occlusion, increases in intraocular pressure, and arterial thromboembolic events have occurred following intravitreal injections with BEOVU.

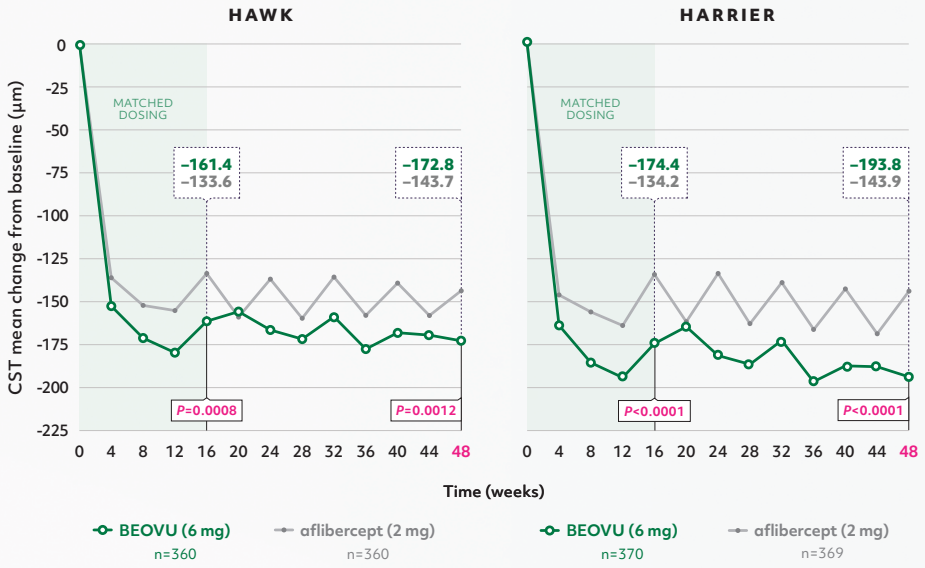
The most common adverse events (≥5% of patients) with BEOVU were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain.

REFERENCES: 1. Beovu [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Dugel PU, Koh A, Ogura Y, et al, on behalf of the HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84. **3.** Data on file. RTH258-C001 Clinical Study Report. Novartis Pharmaceuticals Corp; December 2018. **4.** Data on file. RTH258-C002 Clinical Study Report. Novartis Pharmaceuticals Corp; December 2018. **5.** Data on file. RTH258-C001 & RTH258-C002 CST. Novartis Pharmaceuticals Corp; September 2019.

Learn more at **BEOVUhcp.com**

Greater CST reductions[2]

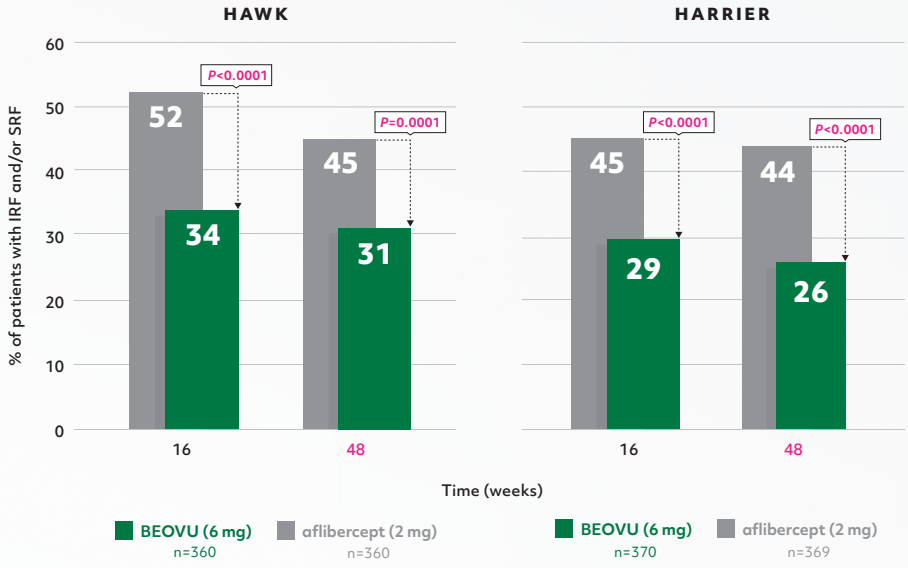
Secondary endpoint: CST reductions with BEOVU vs aflibercept from baseline to Week 48[2-5]



In HAWK, superior CST reductions were achieved at Week 16 and Week 48. In HARRIER, *P* values are nominal and not adjusted for multiplicity.[2] Clinical significance has not been established. No conclusions of efficacy may be drawn.

Fewer patients with IRF and/or SRF[2]

Secondary endpoint: % of patients on BEOVU with IRF and/or SRF vs aflibercept at Weeks 16 and 48[3,4]



In HAWK, superior reductions in the percentage of patients with IRF and/or SRF were achieved at Week 16 and Week 48. In HARRIER, *P* values are nominal and not adjusted for multiplicity.[2] Clinical significance has not been established. No conclusions of efficacy may be drawn.

IMPORTANT SAFETY INFORMATION (cont)

ADVERSE REACTIONS (cont)

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU. The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following page.

NOVARTIS

Beovu® (brolucizumab-dbll) Injection

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

BEOVU® (brolucizumab-dbll) injection, for intravitreal use
Initial U.S. Approval: 2019

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

1 INDICATIONS AND USAGE

BEOVU® is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

BEOVU is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

BEOVU is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

BEOVU is contraindicated in patients with known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachment

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachment *[see Contraindications (4.1) and Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately *[see Dosage and Administration (2.4) and Patient Counseling Information (17) in the full prescribing information]*.

5.2 Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of BEOVU *[see Contraindications (4.2) and Adverse Reactions (6.1)]*. Patients should be instructed to report any change in vision without delay.

5.3 Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection, including with BEOVU *[see Adverse Reactions (6.1)]*. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately *[see Dosage and Administration (2.4) in the full prescribing information]*.

5.4 Thromboembolic Events

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

The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms *[see Clinical Studies (14.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4.3)]*
- Endophthalmitis and Retinal Detachment *[see Warnings and Precautions (5.1)]*
- Retinal Vasculitis and/or Retinal Vascular Occlusion *[see Warnings and Precautions (5.2)]*
- Increase in Intraocular Pressure *[see Warnings and Precautions (5.3)]*
- Thromboembolic Events *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

A total of 1088 patients, treated with brolucizumab, constituted the safety population in the two controlled neovascular AMD Phase 3 studies (HAWK and HARRIER) with a cumulative 96 week exposure to BEOVU, and 730 patients treated with the recommended dose of 6 mg *[see Clinical Studies (14.1) in the full prescribing information]*.

Adverse reactions reported to occur in ≥ 1% of patients who received treatment with BEOVU pooled across HAWK and HARRIER, are listed below in Table 1.

Table 1: Common Adverse Reactions (≥ 1%) in the HAWK and HARRIER wet AMD Clinical Trials

Adverse Drug Reactions	BEOVU (N = 730)	Active Control (aflibercept) (N = 729)
Vision blurred[a]	10%	11%
Cataract	7%	11%
Conjunctival hemorrhage	6%	7%
Vitreous floaters	5%	3%
Eye pain	5%	6%
Intraocular inflammation[b]	4%	1%
Intraocular pressure increased	4%	5%
Retinal hemorrhage	4%	3%
Vitreous detachment	4%	3%
Conjunctivitis	3%	2%
Retinal pigment epithelial tear	3%	1%
Corneal abrasion	2%	2%
Hypersensitivity[c]	2%	1%
Punctate keratitis	1%	2%
Retinal tear	1%	1%
Endophthalmitis	1%	< 1%
Blindness[d]	1%	< 1%
Retinal artery occlusion	1%	< 1%
Retinal detachment	1%	< 1%
Conjunctival hyperemia	1%	1%
Lacrimation increased	1%	1%
Abnormal sensation in eye	1%	2%
Detachment of retinal pigment epithelium	1%	< 1%

[a]Including vision blurred, visual acuity reduced, visual acuity reduced transiently, and visual impairment.
[b]Including anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorioretinitis, eye inflammation, iridocyclitis, iritis, retinal vasculitis, retinal vascular occlusion, uveitis, vitreous haze, vitritis.
[c]Including urticaria, rash, pruritus, erythema.
[d]Including blindness, blindness transient, amaurosis, and amaurosis fugax.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. The immunogenicity of BEOVU was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to BEOVU in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BEOVU with the incidence of antibodies to other products may be misleading.

Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU.

The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BEOVU administration in pregnant women.

Based on the anti-VEGF mechanism of action for brolucizumab *[see Clinical Pharmacology (12.1) in the full prescribing information]*, treatment with BEOVU may pose a risk to human embryo-fetal development. BEOVU should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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

Data

Animal Data
VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility.

8.2 Lactation
Risk Summary
There is no information regarding the presence of brolucizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are transferred in human milk and because of the potential for absorption and adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with BEOVU.

8.3 Females and Males of Reproductive Potential
Contraception

Females
Females of reproductive potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BEOVU and for at least one month after the last dose when stopping treatment with BEOVU.

Infertility
No studies on the effects of brolucizumab on fertility have been conducted and it is not known whether brolucizumab can affect reproductive capacity. Based on its anti-VEGF mechanism of action, treatment with BEOVU may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and efficacy of BEOVU in pediatric patients has not been established.

8.5 Geriatric Use
In the two Phase 3 clinical studies, approximately 90% (978/1089) of patients randomized to treatment with BEOVU were ≥ 65 years of age and approximately 60% (648/1089) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is required in patients 65 years and above.

Manufactured by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
U.S. License Number: 1244

T2020-81

The New Frontier: Gene Therapy for AMD

Clinical trials, although in the earliest phases, are showing exciting results. How might these treatments impact your practice in the future?

A DISCUSSION WITH ROBERT L. AVERY, MD; PETER CAMPOCHIARO, MD, PHD; JEFFREY S. HEIER, MD; SZILÁRD KISS, MD; AND CHARLES WYKOFF, MD, PHD; MODERATED BY ALLEN C. HO, MD

Allen C. Ho, MD: Gene therapy has gone from science fiction to science fact. Although many retina specialists don't use gene therapy right now, there is an approved therapy, Spark Therapeutics' voretigene neparvovec (Luxturna), for Leber congenital amaurosis biallelic RPE65 mutation.

Gene therapy has evolved from gene replacement for an inherited retinal degeneration to gene therapy to create a potential ocular biofactory for more common retinal conditions—for example, anti-VEGF therapy for AMD or diabetic retinopathy. We have significant history here and failed trials. For example, Avalanche for exudative AMD did not work, but there are multiple learnings from Avalanche and other first-generation gene therapy trials that have improved our next-generation clinical trials.

DR. HO: WHERE ARE WE TODAY WITH NEXT-GENERATION CLINICAL TRIALS AND THERAPIES?

Charles Wykoff, MD, PhD: There are currently two therapeutics in human clinical trials evaluating treatment for exudative retinal diseases. They work by establishing an intraocular biofactory that produces an anti-VEGF protein. ADVM-022 (Averum Biotechnologies) produces aflibercept following an intravitreal injection, and RGX-314 (Regenxbio) produces ranibizumab following either subretinal or suprachoroidal delivery.

Both gene therapies are being actively studied in wet AMD, and studies have enrolled patients who are anti-VEGF responsive and have, on average, received years of repeated intravitreal anti-VEGF injections prior to gene therapy treatment. ADVM-022 is in a phase 1 trial involving 30 patients, and RGX-314 is in a phase 1/2a trial involving 42 patients.

So far, we've seen strong efficacy signals in both of these programs and identified important safety signals, some of which were unexpected. Both programs appear to be moving forward in wet AMD, and both are investigating other exudative retinal diseases including diabetic retinopathy and diabetic macular edema (DME).

DR. HO: WHY DO THESE TRIALS SEEM TO BE DOING BETTER THAN THE FIRST-GENERATION TRIALS FOR WET AMD?

Jeffrey S. Heier, MD: We've learned a lot from the earlier trials. They initially looked at gene therapy in terms of the product loads. We saw certain levels of efficacy and issues such as lower expression and less-than-ideal delivery. For instance, Genzyme had a study that looked at a soluble sFLT1 with an AAV2 vector, and we didn't get the level of efficacy that we wanted. In addition, Avalanche didn't have quite the desired efficacy, likely due to issues with the delivery method.

We've taken the lessons from each of those and developed better vectors and standardized approaches to gene therapy delivery. That has enabled us to achieve greater efficacy and improved delivery of the gene therapy product.

DR. HO: AAV2 IS THE FDA APPROVED VIRAL VECTOR FOR SUBRETINAL DELIVERY OF VORETIGENE NEPARVOVEC. WHAT DO WE KNOW ABOUT AAV2 AND ITS TRANSFECTION AND TRANSDUCTION EFFICIENCY?

Peter Campochiaro, MD, PhD: Viruses are good at getting into cells and getting into the nucleus. The viral capsid binds to certain molecules to enter a cell, and different serotypes of AAV bind to different molecules on the surface.

AAV2 binds to heparan-sulfate proteoglycan, which is abundant in the subretinal space. As a result, AAV2 injected into the subretinal space easily enters photoreceptors and retinal pigment epithelium cells. But when you inject AAV2 into the suprachoroidal space, there's not as much heparan-sulfate proteoglycan on the basal surface of retinal pigment epithelium cells compared with the apical surface, and it doesn't enter very well. In the vitreous cavity, the problem is the internal limiting membrane; AAV2 binds to it, which prevents AAV2 from easily entering the retina to transduce cells.

DR. HO: WHAT IS THE CURRENT STATUS OF ADVERUM'S PROGRAM?

Szilárd Kiss, MD: Viral vectors currently being used in patients come in two broad forms. There are the naturally occurring vectors, either human serotypes such as AAV2, AAV8, and AAV9 or primate serotypes such as rhesus isolate 10. Then there are vectors that do not occur in nature but have been engineered for specific routes of administration or cellular tropism.

Adverum has overcome the challenges of retinal transduction posed by intravitreal injections with a novel vector, AAV7m8. This vector was engineered from AAV2 through directed evolution specifically for its ability for retinal transduction following intravitreal injection. Insertion of a peptide sequence in the viral capsid of AAV2 changes the binding properties of the vector, allowing intravitreal delivery.

Adverum's OPTIC and INFINITY programs use the vector construct ADVM-022, which uses AAV7m8 with a transgene encoding aflibercept. The concept here is to allow AAV7m8 to be administered via an in-office intravitreal injection to transduce the retinal cells to make sufficient quantities of aflibercept to control disease activity in patients with VEGF-mediated retinal disorders such as wet AMD and DME.

The OPTIC trial enrolled wet AMD patients in four cohorts at two vector doses. These patients required frequent anti-VEGF injections to maintain visual acuity and control disease activity. Recent top-line data from OPTIC indicate that ADVM-022 provides durable and sustained efficacy at both doses. Patients maintained or gained vision and had stable or improved retinal anatomy seen on OCT. In patients who consented to anterior chamber taps, aflibercept protein expression was within the targeted therapeutic range and was stable out to 104 weeks following a single ADVM-022 injection.

Following ADVM-022 injection, there was an 85% to 96% reduction in annualized injection frequency.

AT A GLANCE

- Regenxbio's phase 1/2a trial for RGX-314 has up to 3 years of data for patients in cohort 3 with sustained visual gain and stable anatomy over time and sustained protein results at 2 years. At 1.5 years after RGX-314 treatment, patients in cohort 4 saw stable vision and improved anatomy with a 58.3% reduction in anti-VEGF treatment burden; patients in cohort 5 saw a reduction of 81.2%.
- Long-term data from Adverum's OPTIC clinical trial for ADVM-022 showed durable expression of aflibercept following a single intravitreal injection of ADVM-022 for both doses; at 1 year, 60% of patients were injection-free following treatment with the low dose with an 85% reduction in annualized injection frequency.
- In the 12 to 48 weeks after administration of GT005 (Gyroscope) in the phase 1/2 open-label FOCUS trial, nine of 10 patients treated with GT005 had increases in vitreous complement factor I levels, with an average increase of 146% compared with baseline.

Patients in OPTIC did require steroid treatment to control what appeared to be dose-dependent intraocular inflammation following administration. Patients in the low dose cohort responded well to a topical steroid regimen, whereas the higher dose patients required longer duration therapy.

Adverum's other ongoing clinical trial, INFINITY, enrolled patients with visually significant DME, and the company recently announced the occurrence of a suspected unexpected serious adverse reaction (SUSAR) 30 weeks after a patient received the high dose. Other than vision loss and hypotony, the specifics surrounding this SUSAR are still being evaluated. Fortunately, it does not appear that any patients enrolled in OPTIC experienced similar adverse events. Nonetheless, the occurrence of just one such event should make us take pause to ensure the safety of all clinical trial patients.

DR. HO: WHAT ARE THE HIGHLIGHTS OF THE REGENXBIO PROGRAM?

Robert L. Avery, MD: Regenxbio evaluated five dosing cohorts of RGX-314, all without significant inflammation. In the three highest dose cohorts, there was a significant reduction in anti-VEGF treatment burden, with reduction by more than 80% in cohort 5. Cohort 3 has 3 years of follow up, and there is retinal stability with a mean increase of 12 letters of

visual acuity. Aqueous taps demonstrated a dose-dependent expression of ranibizumab-like protein levels across all cohorts at 1 year, with stability out to 2 years in cohort 3. One significant side effect noted was pigmentary changes in the inferior periphery, mostly in the higher doses.

Subretinal injection offers both advantages and disadvantages. Although you have to take the patient to the OR, the subretinal space is more immune-privileged, and we haven't seen any significant inflammation thus far. The disadvantage is the need to perform vitrectomy, but suprachoroidal delivery is being evaluated and could obviate this need if it is efficacious. This would be beneficial not only for the elderly patient who doesn't want to have an operation, but also for young diabetic patients who, were they to have surgery, might develop cataracts earlier in life.

DR. HO: HAVE WE SEEN RETINAL VASCULITIS OR INFLAMMATION IN THE ADVERUM PROGRAM?

Dr. Kiss: A limited anterior and vitreous inflammatory response has been noted with ADVM-022 administration. From the available data, this seems to be dose-dependent, with the higher vector doses leading to a more prolonged inflammation that requires more steroid and a longer duration of treatment. I am not aware of any instances of retinal vasculitis, retinal vascular occlusion, or retinitis/choroiditis in any of the patients treated with ADVM-022. The major caveat, of course, is that we don't have the full analysis of the recently reported SUSAR in one patient in the INFINITY trial.

DR. HO: IF A GENE THERAPY WERE TO BECOME AVAILABLE, WHERE DO YOU THINK THIS WOULD FIT IN YOUR PATIENT POPULATION?

Dr. Wykoff: The more tools in our toolbox, the better. We're moving in a direction where individualized therapy is going to become more important than ever as the number of approved pharmaceuticals and devices increases.

In the context of gene therapy for wet AMD, we are still looking at early stage data for both ADVM-022 and RGX-314. Long-term efficacy and safety outcomes will be critical. The broader field of medical science has been overpromising gene therapies for too long. I'm a little hesitant to do that now. These are complicated therapies, and the way they are changing the intraocular environment is still incompletely understood. We're looking at promising phase 1/2a data, and we have a tremendous amount still to learn before the commercialization of gene therapy for wet AMD.

DR. HO: WHAT IS THE LATEST STRATEGY TO IMPROVE GENE THERAPY DELIVERY TO THE SUBRETINAL SPACE WITHOUT A RETINOTOMY?

Dr. Heier: For this technique, a scleral incision allows entry to the suprachoroidal space. A thin, well-designed, flexible cannula is guided posteriorly until it gets close to the arcades. When it is in the desired position, a curved needle enters the subretinal space and the gene therapy product is injected without exposure to the intraocular space. This took several years to design and to make it safe and reproducible. The elegance of this approach is that you don't enter the intraocular cavity. You're not running the risk of inducing cataracts, you're not allowing the therapy into the vitreous cavity to cause untoward effects, and you're delivering into the space that you believe will allow the best expression.

Again, the more weapons we have in our arsenal—the more delivery methods we have—the greater the likelihood of achieving success in the long run.

DR. HO: I'VE TOLD MY PATIENTS, "I HAVE NO WEAPON TO FIX AGING IN YOUR EYE. EVEN IF YOU HAVE WET MACULAR DEGENERATION, I MIGHT BE ABLE TO CONTROL THE LEAKAGE, BUT NOT THE ATROPHY." NOW WE HAVE A GENE THERAPY THAT'S EXPLORING THIS. WHAT ARE YOUR INSIGHTS ON THIS?

Dr. Wykoff: It makes a lot of sense to use gene therapy to manage geographic atrophy (GA), and I can see this eventually being more clinically applicable than gene therapy for wet AMD. Anti-VEGF pharmacotherapies have changed the epidemiology of blindness in many countries, and GA has emerged as a tremendous unmet need.

The Gyroscope approach is to deliver a vector designed to overexpress complement factor I, which is a natural downregulator of complement activity. The team is using a unique subretinal delivery approach via the suprachoroidal space. The goal in this case is not to completely shut down the complement cascade by inhibiting C3 or C5, which are both being studied in global phase 3 programs; rather, the goal is to limit overactivation of the complement cascade while allowing some natural physiologic activity. It's an elegant, targeted approach in early stage clinical trials, whose future likely partially depends on the results of the ongoing phase 3 trials studying C3 and C5 inhibition; if those do not work, it seems unlikely that upregulation of complement factor I would work to slow GA progression.

DR. HO: IT'S INTERESTING THAT APELLIS AND IVERIC ARE SHOWING AN INCREASED RISK OF CHOROIDAL NEOVASCULARIZATION AS A POTENTIAL SIDE EFFECT OF TREATMENT. IT TELLS ME THAT SOMETHING MAY BE WORKING. IS THAT TRUE?

Dr. Campochiaro: It suggests that choroidal neovascularization may be adaptive. There's dropout of the choriocapillaris that causes ischemia of the outer retina. If severe, that results in GA. If less severe, you get hypoxia of the outer retina, which stimulates increased VEGF and choroidal neovascularization. In these programs where you're inhibiting or slowing GA, you may be allowing that tissue to be less ischemic. As a result, you get more upregulation of VEGF and more choroidal neovascularization.

In addition, in patients who are treated with anti-VEGF agents, those who develop macular atrophy frequently develop it in areas where choroidal neovascularization has regressed. This suggests that choroidal neovascularization was

providing some benefit to that tissue. We should keep an open mind about that. I would be fine trading a treatable component of the disease for a previously untreatable component.

DR. HO: HOW IS THE SYSTEM GOING TO PAY FOR THIS?

Dr. Avery: We don't know for sure. Currently approved gene therapies are very expensive but are for rare conditions. For common diseases, the price will have to be less. Billions are spent on anti-VEGF agents each year, and some justification for pricing could come from a reduction in these costs. A reduction in patient visits and overall treatment burden would be attractive, as would less concern about compliance. Theoretically, constant delivery could yield better outcomes, but this remains to be seen. Regardless, whether this becomes cost-effective compared with injections depends upon pricing, which will likely be contentious. But these therapies could potentially provide a huge benefit for patients.

Dr. Ho: The demand for improved therapies for common diseases such as AMD and diabetic retinopathy is infusing resources into our retina clinical trial ecosystem. We have companies such as Adverum, Regenxbio, and Gyroscope, among others, but also major pharmaceutical companies that are just beginning to look at the major retinal diseases. AbbVie/Allergan, Roche/Genentech/Spark, and Johnson & Johnson/Janssen, to name a few, have entered the arena, so we will have even greater opportunity to innovate and improve treatments for patients. Vision matters, and we have demographic trends such as an aging population and a global diabetes pandemic driving the need for better treatments. Many gene therapy industry leaders are not focused only on the science; they believe the science will work. They're challenged by the reimbursement and payment structure. There are hurdles in science, clinical trials, potential commercial execution, and in rewarding those who bring these to market—but ultimately the patients tell us that these therapies are very important because vision is so integral to quality of life.

DR. HO: ANY SUMMARY THOUGHTS FOR OUR READERS?

Dr. Heier: If ever there was a role for gene therapy, it would be for dry AMD. We treat wet AMD, but many of us recognize that the treatment burden leads to undertreatment. Fortunately, we have biomarkers (ie, OCT and retinal fluid) that can guide us, hopefully minimizing the extent of undertreatment. There is no possibility for doing that in dry AMD. If the study says you have to treat monthly, you have to treat monthly forever. So gene therapy could be ideal for the long-term treatment of dry AMD.

Dr. Kiss: We've entered a new realm of gene therapy as a drug delivery platform. We are not taking an abnormal gene and trying to fix it; we're using gene therapy as a therapeutic platform to deliver drugs to the eye.

It's exciting, but it's early. The Regenxbio and Adverum programs are now entering pivotal trials, which might be the first time that has happened for gene therapy as a drug delivery platform in any field of medicine.

Dr. Campochiaro: In trials testing gene therapy for wet AMD, we're learning things that are going to help in other areas. For instance, most of the gene therapies in the eye are with transgenes that aren't soluble, so it's difficult to know how much transgene is being expressed and for how long. With Leber congenital amaurosis, we must rely on how a patient responds with regard to mobility and measures of visual function to assess whether expression is occurring. But with these wet AMD programs we can measure the transgene. We're learning for the first time if this going to be a one and done treatment or if efficacy is going to wane.

Dr. Wykoff: It is worth noting that, as far as I know, there have been no nonocular adverse events attributable to these ocular gene therapies, which is important. From a systemic perspective, there are no concerning signals so far, which is very encouraging.

Dr. Avery: The eye is an excellent organ for advancing gene therapy. It's a self-contained organ with a nice window through it, allowing our great tools to evaluate it. We've had a lion's share of advances, and I think we'll continue to see more because the eye is such a good model for developing gene therapy.

Dr. Ho: It's a real privilege to have these partners, colleagues, and friends on this journey. Our goal here has been to provide an overview of why and how gene therapies may become relevant tools. Sometimes this road has unexpected turns and hazards, but early data from phase 1/2 programs are showing promise. We must continue to do the work of evolving viral vectors, understanding immune responses, improving delivery methods, and more. Because vision is so highly valued in quality of life evaluations, improved therapies for common conditions such as AMD and diabetic retinopathy will find their place in our toolbox. For those of you who aren't up to date on gene therapy, we hope this discussion has piqued your interest to look for papers, presentations, and podcasts on this topic. Stay on course, as the story will continue to unfold. ■

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

(Continued on page 30)

Monitoring For Wet AMD in the Fellow Eye

Extended treatment intervals may affect disease detection. Here's what you can do to catch it early.

BY BYRON LADD, MD, AND MIGUEL BUSQUETS, MD

The next wave of therapeutic innovation for the treatment of wet AMD is focused on increasing treatment intervals to reduce patient burden and improve compliance. Retina specialists have increasingly employed treat-and-extend (TAE) regimens, which can significantly reduce treatment burden without sacrificing visual gains compared with monthly injection intervals.[1]

However, fewer visits also mean that patients with unilateral wet AMD receive fewer examinations of their fellow eye. This presents retina specialists with a conundrum: How do we alleviate treatment burden while also monitoring fellow eyes for disease conversion?

FELLOW EYE DETECTION

A 2020 study by Ho et al found that wet AMD patients in the AAO IRIS Registry who presented with higher visual acuity at baseline maintained higher visual acuity at 1 and 2 years.[2] Ying et al found similar results in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT; Figure 1).[3] The conclusion by Ho et al—patients with at least 20/40 VA at baseline are most likely to maintain that level of vision at 2 years—gives retina specialists a goal: Detect wet AMD in eyes with at least 20/40 VA to keep vision at a functional level.

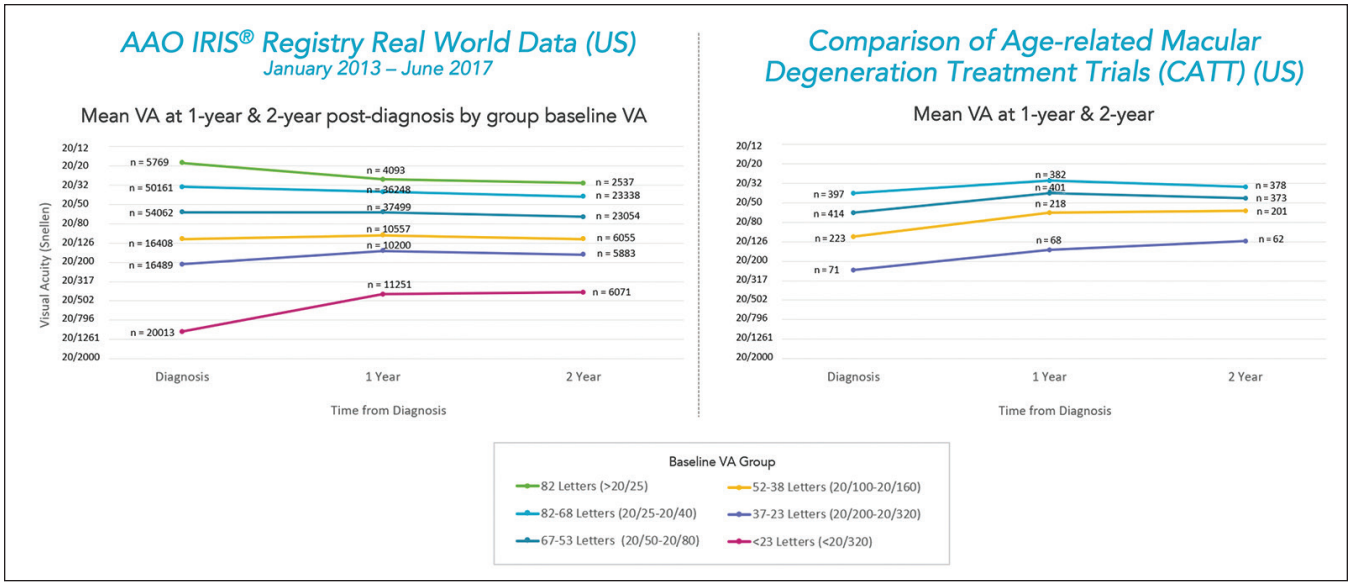
Interestingly, 20/40 VA is not an arbitrary cutoff point determined by data. Instead, it is the threshold for reading, watching television, performing daily activities, and, for many states, the visual acuity required to drive.

Unfortunately, real-world data indicate that the vision of patients with newly diagnosed wet AMD is often below this threshold, at a mean of 20/85 and 20/79 for the first and second eyes (Table 1).[2] Only 33% of first eyes and 36% of second eyes diagnosed with wet AMD have at least 20/40 VA, suggesting that a majority of fellow eyes, even with frequent visits, are not diagnosed until VA is well below 20/40.

Part of the problem may be the rapid rate at which wet

AT A GLANCE

- Because treat-and-extend regimens require fewer visits, patients with unilateral wet AMD receive fewer examinations of their fellow eye.
- Patients with at least 20/40 VA at baseline are most likely to maintain that level of vision after 2 years of treatment; however, only 33% of first eyes and 36% of second eyes newly diagnosed with wet AMD have at least 20/40 VA.
- Among eyes with at least 20/40 VA at baseline, 81% maintained 20/40 VA when wet AMD disease activity was detected by the ForeseeHome AMD Monitoring Program (Notal Vision).



Graphic courtesy of Natal Vision

Figure 1. Both the AAO IRIS Registry study and CATT determined that patients with wet AMD whose disease was detected early had better visual function at 1 and 2 years.

AMD develops. In our experience, some patients who develop contralateral AMD do not demonstrate disease activity on routine examination but present a week later with active disease that has pushed VA below 20/40. Further, expanded use of TAE regimens and the possible proliferation of extended-duration therapies mean that a new method of disease monitoring is needed between office visits.

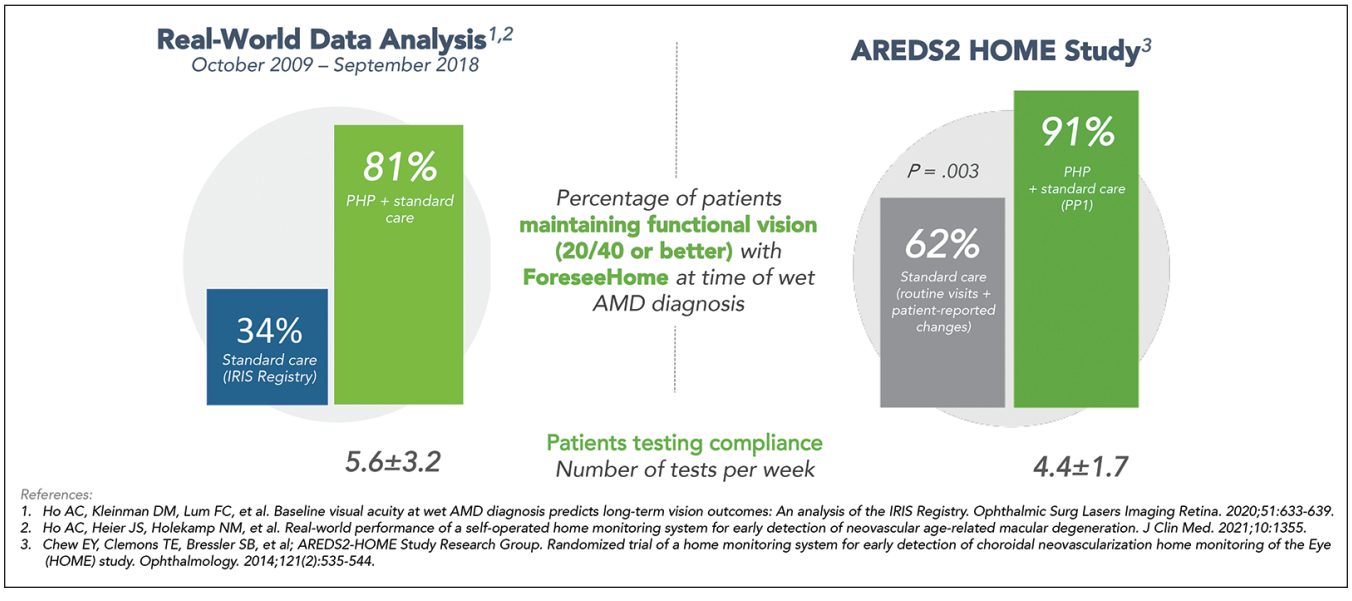
Patients being treated for wet AMD in one eye often ask how they can prevent vision loss in their other eye, underscoring what quality-of-life surveys have already shown us: Severe vision loss can be as debilitating as conditions such as uncontrolled pain due to cancer, home dialysis, and stroke.[4]

(Continued on page 29)

TABLE 1. BASELINE VA AND PERCENTAGE OF EYES WITH ≥ 20/40 VA AT DIAGNOSIS

	Mean VA at Diagnosis	% of Eyes with ≥ 20/40 Baseline VA
All eyes	20/83	34%
First eyes	20/85	33%
Second eyes	20/79	36%

Adapted from: 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(11):633-639.



Graphic courtesy of Natal Vision

Figure 2. ForeseeHome real-world performance resembled pivotal trial results.

HOME-BASED AMD MONITORING: THE REAL-WORLD DATA

BY JEFFREY S. HEIER, MD

Clinicians often have great expectations for drugs and technologies that have been shown to be safe and effective in clinical trials. Unfortunately, many fail to live up to that potential in real-world application. There are many hypotheses for the differences between performance in the trial setting and the clinic; most focus on undertreatment and an inability to follow patients as closely in the real world as in clinical trials.

It is noteworthy, then, when data from a real-world study closely align with those from a clinical trial. A 2021 real-world evaluation of the efficacy of the ForeseeHome AMD Monitoring Program (Notal Vision) for detecting conversion from intermediate to wet AMD found that adding home monitoring to the standard of care was an effective method for identifying potential disease progression.[1] The data and conclusions were similar to those found in the pivotal AREDS2-HOME clinical trial that first evaluated the ForeseeHome in patients with intermediate AMD.[2]

TABLE 1. PATIENT DEMOGRAPHICS AND MODALITY TRIGGERING DETECTION

	Total (N = 306)	At-Home Monitoring Alert	During Routine Visit or By Patient Symptoms
Modality triggering detection, n (%)	306	211 (69%)	95 (31%)
Age, mean (standard deviation)	75 (7.1)	76 (6.9)	73 (7.3)
Women, n (%)	199 (65%)	139 (66%)	60 (63%)

TABLE 2. MEDIAN VA AT BASELINE AND EVENT, AND VA CHANGE

	Baseline VA	Event VA	Event VA if Baseline VA available	VA change
All Eyes With Known VA				
Eyes, n	121	193	121	
Median VA, letters (Snellen)	79 (20/25-2)	75 (20/32-1)	74 (20/32-2)	-3
Eyes With CNV Event Detected By ForeseeHome With Known VA				
Eyes, n	95	151	95	
Median VA, letters (Snellen)	78 (20/32+2)	75 (20/32-1)	74 (20/32-2)	-2
Eyes With CNV Event Detected By Other Means With Known VA				
Eyes, n	26	42	26	
Median VA, letters (Snellen)	81 (20/25)	76 (20/32)	74 (20/32-2)	-4.5

STUDY OVERVIEW

My colleagues and I performed a retrospective review of patients whose data were collected in the electronic health records of the Notal Vision Diagnostic Clinic, ForeseeHome's monitoring service. We included patients who had a valid device baseline test and at least 20/60 VA in any eye prescribed the ForeseeHome program. A total of 306 patients had confirmed conversion from intermediate AMD to wet AMD.

The monitoring regimen in this real-world study comprised use of the ForeseeHome device, routine examination, and examination triggered by symptoms. Of the 306 patients in the study who converted to wet AMD, 69% had their disease detected by the ForeseeHome device (Table 1).

Median baseline VA for all study patients was 79 letters (20/25-2). When progression to wet AMD was detected, median VA was 75 letters (20/32-1), an average VA change of only 3 letters (Table 2).

Given that Ho et al found that patients who presented with wet AMD and at least 20/40 VA at baseline maintained that level of visual acuity at 2 years if they underwent intravitreal anti-VEGF therapy,[3] we examined the percentage of patients who had at least 20/40 VA at baseline and remained at least at 20/40 when disease was detected.

Of the 109 patients with at least 20/40 VA at baseline, 88 (81%) retained

at least 20/40 VA when wet AMD was detected by any method. This real-world finding confirmed the results of the AREDS-2 HOME study, in which 91% of patients maintained this level of functional vision.[2] Although the percentage of disease detection in the real world was higher in the device subgroup, there was no statistical difference between the device and routine or symptomatic examination subgroups. The attentiveness and disease awareness raised by the patient education program provided by the remote diagnostic clinic likely contributed to this positive finding compared with standard of care, which typically lacks remote engagement (Table 3).

TABLE 3. EYES MAINTAINING VA ≥ 20/40 AT CONVERSION

	Entire Cohort	Detected Following a Device Alert	Detected During Routine Office Visit/By Patient Symptoms
Eyes with VA ≥ 20/40 at baseline, n	109	86	23
Eyes that retained VA ≥ 20/40 at conversion, n (%; 95% CI)	88 (81%; 72%-88%)	71 (83%; 73%-90%)	17 (74%; 52%-90%)

CLINICAL IMPLICATIONS

Reliance on in-office examination and patient self-reported symptoms alone exposes patients to the risk of undetected, asymptomatic onset of wet AMD for, potentially, an extended period of time in a real-word setting. A monitoring regimen that includes home-based digital health technology can help fill the systematic gap office-based medicine is confronted with every day.

Continued monitoring (ie, a combination of home-based monitoring and routine/symptomatic clinical examinations) of patients with intermediate AMD may help clinicians detect conversion to wet AMD. Catching disease in patients before visual acuity dips below 20/40 is key to preserving vision in patients through long-term therapy.

In this real-world study, a home-based/examination-based hybrid monitoring program was found to be effective, reinforcing the findings of the clinical trial. The support and disease education a remote diagnostic clinic provides to patients between office visits also helps drive compliance and success. Digital health solutions provided in partnership with traditional office-based care can help protect vision in at-risk patients. ■

1. Ho AC, Heier JS, Holekamp NM, et al. Real-world performance of a self-operated home monitoring system for early detection of neovascular age-related macular degeneration. *J Clin Med*. 2021;10(7):1355.
2. Chew EY, Clemons TE, Bressler SB, et al; AREDS2-HOME Study Research Group. Randomized trial of the ForeseeHome monitoring device for early detection of neovascular age-related macular degeneration. The home monitoring of the eye (HOME) study design - HOME study report number 1. *Contemp Clin Trials*. 2014;37(2):294-300.
3. 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(11):633-639.

JEFFREY S. HEIER, MD
- Director, Retina Service and Director of Retinal Research, Ophthalmic Consultants of Boston
- Editorial Advisory Board Member, *Retina Today*
- jsheier@eyeboston.com
- Financial disclosure: Scientific Advisory Board (Notal)

(Continued from page 27)

A VIABLE SOLUTION

Educating patients that early detection is key to saving vision is important, and setting up a remote monitoring regimen that supplements in-office examinations could help physicians detect disease activity early.

Real-world evidence suggests that use of the ForeseeHome AMD Monitoring Program (Notal Vision) is an effective means by which to consistently monitor patients for wet AMD activity. A 2021 study found that patients with intermediate AMD undergoing a monitoring regimen that included the ForeseeHome platform and both routine and symptom-based eye examinations were likely to have greater than 20/40 VA when wet AMD was detected.[5] This study confirmed results seen in a pivotal trial assessing the efficacy of the ForeseeHome platform in wet AMD detection.[6]

In the 2021 study, median VA was 20/25-2 among eyes with a known baseline. At the moment that wet AMD disease activity was detected, median VA was 20/32-1. Among eyes with at least 20/40 VA at baseline, 81% maintained 20/40 VA when wet AMD disease activity was detected by ForeseeHome or routine/symptom-based eye examination (Figure 2).[5]

IMPLEMENTATION

Use of a monitoring regimen that includes use of a home-based platform faces two hurdles to implementation: physician hesitancy and patient familiarity.

Clinicians may not prescribe this at-home monitoring program because of the misconception that it will increase their workload and they will be tasked with a daily review of data. In reality, the Notal Vision Diagnostic Clinic, the ophthalmic medical center that provides the ForeseeHome monitoring service, uses artificial intelligence-based technology to determine whether a patient's test warrants alerting the referring practice that an in-person examination may be prudent.

The Notal Vision Diagnostic Clinic works with practices to implement simple procedures that take minimal time in the examination lane for identifying and referring patients, and the monitoring center manages everything including benefits verification, device provisioning and training, and patient engagement and compliance.

Further, costs associated with the ForeseeHome AMD Monitoring Program are covered by Medicare, as this diagnostic system has been cleared by the US FDA.

As for patients, they may be intimidated by new technology. A short introduction to at-home monitoring early in the visit (eg, by a technician) familiarizes patients with the technology and the program, allowing the clinician to re-emphasize the idea during the patient encounter. Patients who wish to have agency in their disease monitoring may be inclined to try at-home monitoring. In addition, reminding patients that testing can be an easy addition to their daily routine may reduce any perceived barriers to use.

WHY WAIT?

The data are clear: Use of the ForeseeHome platform can help to identify wet AMD early enough that patients are likely to retain good vision if they are adherent to therapy. Given that extended-duration therapy and TAE regimens are becoming increasingly popular, we need an adjunct to clinic-based fellow eye examination to help detect the acute onset of late-stage disease. The Notal Vision Diagnostic Clinic and the ForeseeHome AMD Monitoring Program could help to fill that need. ■

1. Wykoff CC, Croft DE, Brown DM, et al; TREX-AMD Study Group. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122(12):2514-2522.
2. Ho AC, Kleinman DM, Lum FC, et al. Baseline visual acuity at neovascular AMD diagnosis predicts long-term vision outcomes: an analysis of the IRIS registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51(11):633-639.
3. Ying G, Maguire MG, Daniel E, et al; Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). Association of baseline characteristics and early vision response with 2-year vision outcomes in the comparison of AMD treatments trials (CATT). *Ophthalmology*. 2015;122(12):2523-31.e1.
4. Yuzawa M, Fujita K, Tanaka E, Wang EC. Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice. *Clin Ophthalmol*. 2013;7:1325-1332.
5. Ho AC, Heier JS, Holekamp NM, et al. Real-world performance of a self-operated home monitoring system for early detection of neovascular age-related macular degeneration. *J Clin Med*. 2021;10(7):1355.
6. Chew EY, Clemons TE, Bressler SB, et al; AREDS2-HOME Study Research Group. Randomized trial of the ForeseeHome monitoring device for early detection of neovascular age-related macular degeneration. The home monitoring of the eye (HOME) study design - HOME study report number 1. *Contemp Clin Trials*. 2014;37(2):294-300.

MIGUEL BUSQUETS, MD
- Retina Surgeon, Retina Associates of Kentucky, Lexington, Kentucky
- mbusquets@retinaky.com
- Financial disclosure: Speaker/Consultant (Notal Vision)

BYRON LADD, MD
- Retina Surgeon, Virginia Eye Institute, Richmond, Virginia
- bsladd@gmail.com
- Financial disclosure: Speaker/Consultant (Notal Vision)

(Continued from page 25)

PETER CAMPOCHIARO, MD, PHD
- Director, Retinal Cell and Molecular Laboratory; Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore
- pcampo@jhmi.edu
- Financial disclosure: Consultant (Asclepix, Ashvattha, Bausch + Lomb, Clearside, Regeneron, Wave Life Sciences); Advisory Board (Aerpio, Allegro, Exonate, Genentech/Roche, Merck, Perfuse); Honoraria (Aerpio, Allegro, Asclepix, Ashvattha, Bausch + Lomb, Clearside, Exonate, Genentech/Roche, Merck, Regeneron, Wave Life Sciences): Investigator/Grant (Aerpio, Ashvattha, Genentech/Roche, Sanofi Genzyme, Mallinckrodt, Oxford Biomedica, Perfuse, Regenxbio); Equity/Cofounder (Allegro, Graybug)

JEFFREY S. HEIER, MD
- Director of Retina Service, Director of Retina Research, Ophthalmic Consultants of Boston
- Editorial Advisory Board Member, *Retina Today*
- jsheier@eyeboston.com
- Financial disclosure: Consultant (4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Aviceda, BVT, Dark Horse, DTx, Eloxx, Galimedix, Genentech, Graybug, Gyroscope, Iveric Bio, jCyte, Kanghong, LensGen, NGM, Novartis, Ocular Therapeutix, OcuTerra, Oxurion, Palatin, Regeneron, Regenxbio, Stealth, Thea, Verseon, Vinci, Voyant); Research Grants (Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hemera, Iveric, Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, Stealth)

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 and Grant Funding (Adverum, Apellis, Asclepix, Clearside, Iveric Bio, Genentech, Gyroscope, Kodiak, Lineage, Regenxbio)

SZILÁRD KISS, MD
- Bob and Dolores Hope - Robert M. Ellsworth, MD, Distinguished Associate Professor in Ophthalmology; Associate Dean, Clinical Compliance; Chief, Retina Service, Weill Cornell Medical College, New York
- Associate Attending Physician, New York-Presbyterian Hospital, New York
- Editorial Advisory Board Member, *Retina Today*
- szk7001@med.cornell.edu
- Financial disclosure: Intellectual Property Related to Ocular Gene and Cellular Therapy; Consultant (Adverum, Gyroscope, Regenxbio, Spark)

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

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".

How Would You Handle These Tough AMD Cases?

Whether it's subretinal hyperreflective material, retinal angiomatous proliferation, or polypoidal choroidal vasculopathy, your colleagues have the answers.

AAO 2020 HIGHLIGHT

These cases were presented at the AAO 2020 Virtual Meeting, as part of the "Challenging Cases in Neovascular AMD" session. Attendees walked away with a better understanding of the possible mechanisms at work and the suitable treatment strategy for each case.

- Luiz Lima, MD, session moderator

TOUGH CASE NO. 1

By Sumit Randhir Singh, MD, and Jay Chhablani, MD

A 69-year-old man presented to the retina clinic with sudden onset loss of vision in the right eye for 1 month. Fundus examination revealed multiple small, hard drusen at the macula in each eye with subretinal hemorrhage at the fovea in the right eye. Swept-source OCT showed the presence of retinal thickening, subretinal hyperreflective material (SHRM)—including subretinal hypereereflective exudation and choroidal neovascular complex—subretinal fluid (SRF), and a shallow fibrovascular pigment epithelial detachment (PED) suggestive of type 2 choroidal neovascularization (CNV) (Figure 1A). OCT angiography (OCTA) of the right eye showed a neovascular net in the outer retina and choriocapillaris.

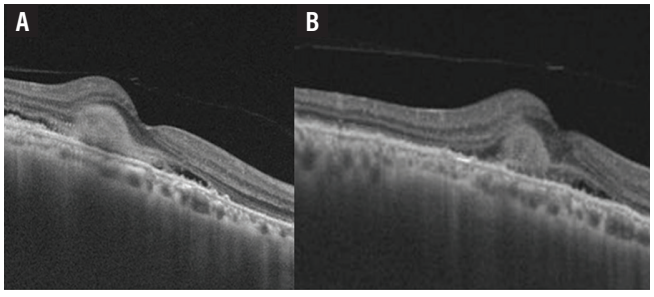


Figure 1. The patient's OCT shows the presence of type 2 CNV and SHRM (A). After two intravitreal injections of ranibizumab and one of IVZ, OCT showed persistent SHRM (B).

The patient received two intravitreal injections of ranibizumab 0.5 mg/0.05 mL (Lucentis, Genentech) at baseline and at 1 month, along with one intravitreal injection of ziv-aflibercept 1.25 mg/0.05 mL (IVZ; Zaltrap, Sanofi) at the end of the second month.

At the 3-month follow-up visit, OCT imaging showed a minimum reduction of the SRF with the persistence of SHRM (Figure 1B).

What would be your next steps? See page 34 for our approach.

TOUGH CASE NO. 2

By Julia Farah Agi, MD, and Michel Eid Farah, MD, PhD

A 65-year-old white woman presented with blurry vision in the right eye for 5 months. At presentation, her VA was 20/400 OD and 20/25 OS. The fundoscopic examination of the right eye showed macular thickening with multiple hard exudates in a circinated pattern (Figure 2A). OCT revealed a PED with SRF and intraretinal thickening in the right eye (Figure 2B). There was a disrupted retinal pigment epithelium (RPE) line at the apex, suggesting a communicating vessel. Fluorescein angiography (FA) and ICG angiography of the right eye demonstrated a vertically diving retinal vessel with retina-retina anastomosis (Figure 3).

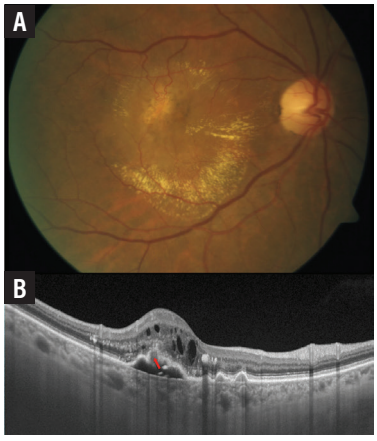


Figure 2. The fundus image of the right eye at presentation (A). The OCT of the right eye at presentation shows a disrupted retinal pigment epithelium (arrow, B).

The fundus images and OCT of the left eye showed drusenoid PEDs with intraretinal fluid (Figure 4). FA of the left eye demonstrated a poorly demarcated area of leakage (Figure 5).

Considering the clinical picture and the multimodal analysis, a diagnosis of retinal angiomatous proliferation (RAP) was established for both eyes.

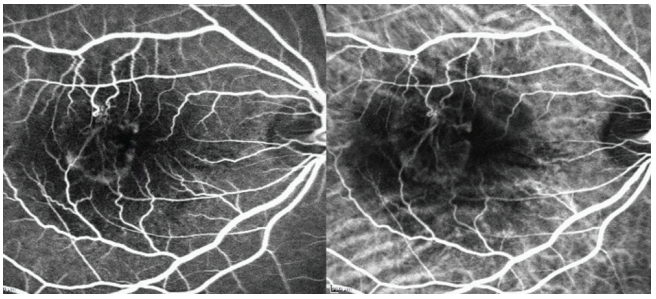


Figure 3. FA and ICG angiography of the right eye showed a vertically diving retinal vessel with retina-retina anastomosis.

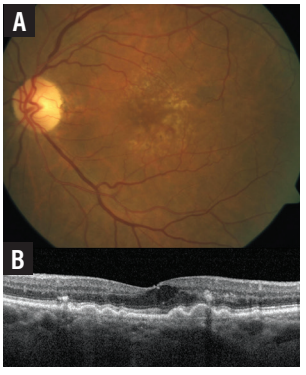


Figure 4. Fundus imaging of the left eye at presentation (A) and the corresponding OCT of the left eye at presentation (B).

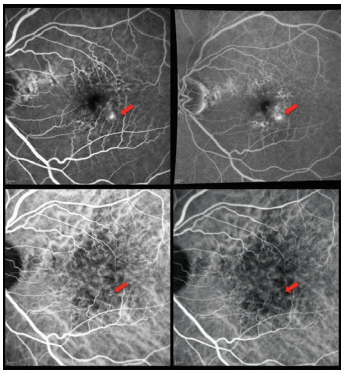


Figure 5. FA and ICG angiography of the left eye revealed a poorly demarcated area of leakage (arrows).

How would you treat this patient? See page 34 for our approach.

TOUGH CASE NO. 3

By Aneesha Kalur, BA, and Rishi P. Singh, MD

A 79-year-old woman presented to the retina clinic in February 2011 with a complaint of gradually decreasing vision in her right eye over the past month. Her medical history included long-standing poor vision in the left eye. BCVA was 20/25-2 OD and counting fingers OS. Ocular history of the left eye showed a hemorrhagic retinal picture with blood and scarring present within the macula. ICG angiography of the right eye showed a hyperfluorescent spot near the optic disc that corresponded with a PED and polypoidal lesions on OCT imaging.

The physician diagnosed the patient with polypoidal choroidal vasculopathy (PCV).

How would you proceed with treatment? See page 34 for our approach.

CASE NO. 1 TREATMENT

Given the persistence of SHRM on OCT, a combination therapy of IVZ and intravitreal triamcinolone acetonide 2 mg/0.05 mL (IVTA) was initiated.

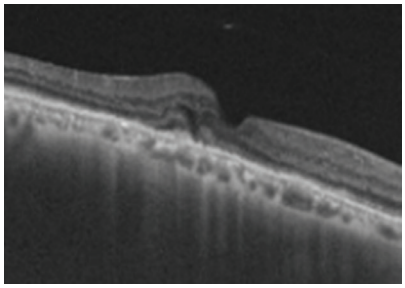


Figure 6. One month after the patient received a combination of IVTA and IVZ, there was reduction of SHRM with no IRF/SRF.

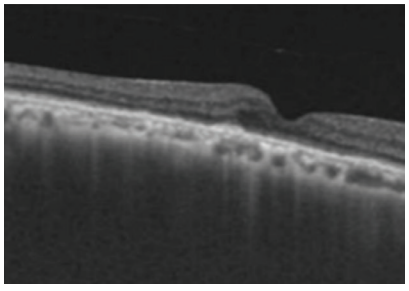


Figure 7. The patient's OCT shows complete resolution at month 6.

At the 4-month follow-up, 1 month after the combination therapy, intraretinal fluid (IRF), SRF, and SHRM completely disappeared and the patient was observed (Figure 6). At month 6, there was complete resolution of IRF, SRF, and SHRM with thinning of the fovea without any recurrence during this period or subfoveal scarring (Figure 7). OCTA of the right eye showed near resolution of the neovascular net. BCVA improved from 20/125 at baseline to 20/60 at month 6.

Although combining anti-VEGF agents with intravitreal steroids has not been shown to have superior results to anti-VEGF monotherapy in wet AMD,[1] adding an intravitreal steroid may help to reduce or resolve SHRM and avoid subretinal scarring, as was the case for this patient.[2]

CASE NO. 2 TREATMENT

After being diagnosed with RAP in each eye, the patient received three intravitreal injections of aflibercept (Eylea, Regeneron) in the right eye followed by a prn regimen; the left eye received only one injection of aflibercept (Figure 8).

The follow-up showed resolution of the retinal fluid and the serous component of the PED; however, a subretinal fibrosis developed in the right eye with partial improvement of VA to 20/200 OD (Figure 9).

After 2 years of observation the patient complained of new onset of vision decline in the left eye. She presented with hard circinated exudates and retinal hemorrhage. OCT revealed reactivation of the RAP lesion. There was intraretinal and subretinal serous fluid, in addition to a significant PED. Three monthly aflibercept injections were performed, and the patient showed significant anatomic response soon after the first injection with improvement of VA to 20/25 OS (Figure 10).

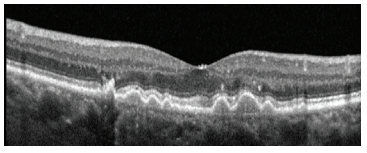


Figure 8. The OCT of the left eye after one injection of an anti-VEGF agent.

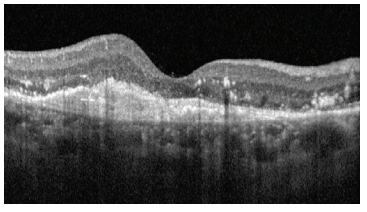


Figure 9. OCT of the right eye after the loading treatment and prn anti-VEGF therapy.

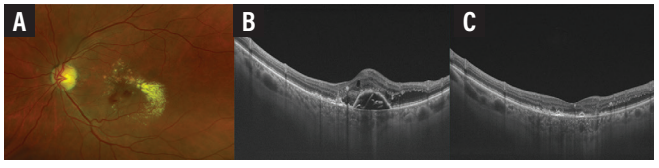


Figure 10. Fundus imaging (A) and OCT 2 years after presentation (B) show exudation in the left eye. OCT imaging after three intravitreal injections of aflibercept shows marked improvements (C).

CASE NO. 3 TREATMENT

This patient with PCV began treatment with an intravitreal injection of ranibizumab in the right eye, followed by photodynamic therapy (PDT) 1 week later, as recommended in the EVEREST II study.[3]

At the 1-month follow-up, BCVA was 20/20 OD, and the patient reported alleviated symptoms. Over the course of 1.5 years, the patient received six doses of ranibizumab and no further PDT. Her vision was subjectively stable at 20/20-1 OD.

The patient received a seventh ranibizumab injection and a second treatment of PDT in September 2013, after which the provider switched to aflibercept injections.

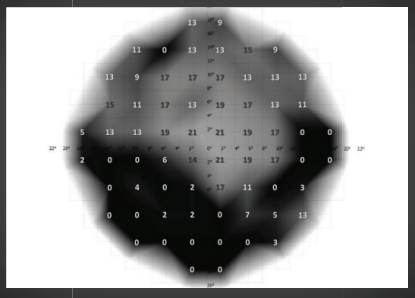
The most recent follow-up in March 2017 showed a BCVA of 20/20 OD. At this point, the patient had received 13 doses of aflibercept, the most recent one given in December 2016. OCT showed no abnormalities at this follow-up. ■

1. Riazi-Esfahani M, Ahmadieh H, Faghihi H, et al. Intravitreal bevacizumab versus combined bevacizumab and triamcinolone acetonide for neovascular age-related macular degeneration. *J Ophthalmic Vis Res*. 2008;3(2):95-101.
2. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Devel Ther*. 2016;10:1857-1867.
3. Koh A, Lai TYY, Takahashi K, et al; the EVEREST II study group. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy a randomized clinical trial. *JAMA Ophthalmol*. 2017;135(11):1206-1213.

SEE WHAT YOU'VE BEEN MISSING!

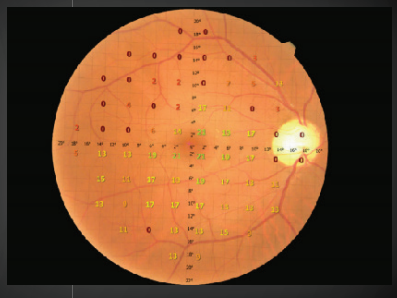
NEW!

Feedback exam for visual rehabilitation



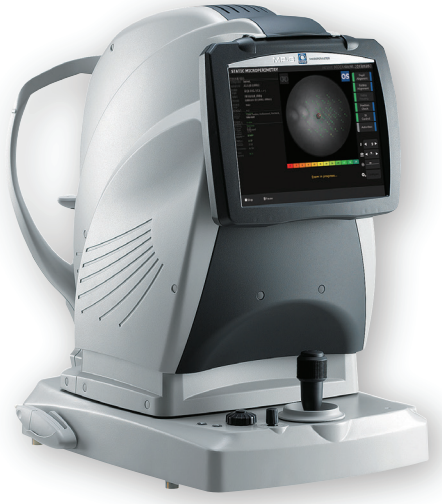
NEW!

Visual sensitivity map in Gray Scale



Wide stimulus & threshold range measurements

MP-3 MICROPERIMETER



Fundus Camera + Visual Field

There have been significant advances in the assessment of retinal morphology due to the introduction of optical coherence tomography (OCT) into clinical practice, however, functional evaluation of retinal pathology is further advanced with the use of microperimetry.

The MP-3 measures local retinal sensitivity for functional assessment of the retina. The results can be displayed over a color fundus image, correlating retinal anatomy to retinal function.

LEARN MORE: info@nidek.com · usa.nidek.com

CALL US TODAY!
1-877-200-9892

Eye & Health Care
NIDEK INC.

April 19, 2021
2021-0014

HOW TO DIAGNOSE AND MANAGE RPE RIPS IN THE SETTING OF AMD

By Amani Fawzi, MD

A rip in the RPE can occur during the course of neovascular AMD therapy, usually in eyes with a vascularized PED or those with type 1 CNV, where it has been reported spontaneously in approximately 10% of eyes. The risk is considered much higher in eyes in which the PED has a large basal diameter or tall PEDs (> 600 µm on OCT poses an approximate 30% risk). A hyperfluorescent ring or halo surrounding a PED on FA may be a telltale sign of an impending RPE rip.[1]

Treatment is generally successful in these eyes, although the sudden development of an RPE rip may be associated with drastic visual consequences when the central fovea is involved. Eyes with high-risk characteristics are at risk for the spontaneous development of an RPE rip, and the risk has been reported to be slightly higher during anti-VEGF therapy. The pathogenesis is thought to be related to contraction of the sub-RPE neovascular tissue, creating tangential stress on the overlying RPE.[2]

One of the main prognostic factors for the visual outcome is the location of the rip; small rips that do not involve the fovea may be associated with excellent vision.[1-3]

An important dilemma that clinicians face is whether to continue therapy once an RPE rip occurs. The widely accepted approach is to continue therapy if there is evidence of ongoing lesion activity, particularly in eyes in which the fovea is preserved.[1]

1. Sarraf D, Joseph A, Rahimy E. Retinal pigment epithelial tears in the era of intravitreal pharmacotherapy: risk factors, pathogenesis, prognosis and treatment (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc*. 2014;112:142-159.
2. Nagiel A, Freund KB, Spaide RF, Munch IC, Larsen M, Sarraf D. Mechanism of retinal pigment epithelium tear formation following intravitreal anti-vascular endothelial growth factor therapy revealed by spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2013;156(5):981-988.e2.
3. Invernizzi A, Nguyen V, Arnold A, Young S, Barthelmes D, Gillies MC. Early and late retinal pigment epithelium tears after anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration. *Ophthalmology*. 2018;125(2):237-244.

AMANI FAWZI, MD
- Professor of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago
- afawzimd@gmail.com
- Financial disclosure: Regeneron, Boehringer Ingelheim, Genentech/Roche

JAY CHHABLANI, MD
- Vitreoretina Specialist, Department of Ophthalmology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
- jay.chhablani@gmail.com
- Financial disclosure: Allergan, Biogen, Salutaris

JULIA FARAH AGI, MD
- Retina Specialist, São Paulo Ophthalmology Center, São Paulo, Brazil
- julialfarah@gmail.com
- Financial disclosure: None

MICHEL EID FARAH, MD, PHD
- Director, São Paulo Ophthalmology Center, São Paulo, Brazil
- Professor, São Paulo Federal University / Paulista School of Medicine, Brazil
- mefarah@me.com
- Financial disclosure: None

ANEESHA KALUR, BA
- Research Fellow, Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland
- axk918@case.edu
- Financial disclosure: None

LUIZ H. LIMA, MD
- Medical Director, Department of Ophthalmology, Universidade Federal de São Paulo, São Paulo, Brazil
- luizlima9@gmail.com
- Financial disclosure: None acknowledged

RISHI P. SINGH, MD
- Director, Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland
- Professor of Ophthalmology, Lerner College of Medicine, Case Western Reserve University, Cleveland
- drrishisingh@gmail.com
- Financial disclosure: Consultant (Alcon, Novartis, Genentech, Regeneron, Bausch + Lomb, Zeiss, Gyroscope); Sponsored Research (Aerie, Apellis, Ocular Therapeutix, Graybug)

SUMIT RANDHIR SINGH, MD
- Vitreo-retina Specialist, Retina and Uveitis Department, GMR Varalakshmi Campus, LV Prasad Eye Institute, Andhra Pradesh, India
- Financial disclosure: None

OCULUS Disposables
For maximum safety and efficiency in the O.R.

- **Always reliable**
  Top performance every time and any place
- **Always sterile**
  Minimized risk of infection and cross-contamination
- **Always fast**
  No sterilization required
- **Always available on the spot**
  Increase your O.R. capacity utilization

We are here for you! Contact us for more information.

Click here to learn more

OCULUS® SURGICAL

Anti-VEGF Therapy: Past, Present, and Future

These agents have fundamentally changed how we care for our patients. Here's my personal perspective on—and role in—the development of the story.

BY ROBERT L. AVERY, MD

Of all the innovations that have improved the practice of retina in the past few decades, the development of anti-VEGF agents has had the most profound impact on our profession and our patients' vision. Here's a look at how it all started and what the future holds.

FACTOR X

The earliest understanding of angiogenesis started in 1948, when I.C. Michaelson, MD, speculated that a diffusible, biologic "factor X" existed in the retina that controlled the growth and development of retinal neovascularization.[1] His theory was accurate, but it didn't start to take hold until 1971, when Judah Folkman, MD, published on the therapeutic implications of anti-angiogenesis.[2]

The search for factor X was taken up by Harold Dvorak, MD, who showed that tumor cells secreted vascular permeability factor. Independently, Napoleone Ferrara, MD, at Genentech, identified vascular endothelial growth factor (VEGF). When both entities were cloned, they turned out to be one and the same molecule, and the VEGF moniker prevailed. Dr. Ferrara pioneered the development of VEGF antibodies, which ultimately developed into bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis, Genentech). Joan W. Miller, MD, and her team in Boston, including Anthony Adamis, MD, and many others, went on to demonstrate the role of VEGF and its inhibition in animal models of retinal disease.

I got swept up into this research just out of residency. In 1993, Lloyd P. Aiello, MD, PhD, previously a resident with me at Wilmer Eye Institute, was working with George L. King, MD, in Boston, and had access to antibodies to this newly discovered proliferative factor. Together, he and I collected and analyzed more than 200 aqueous samples and discovered VEGF concentrations in diabetic retinopathy (DR), vein occlusion, retinopathy of prematurity (ROP), and even chronic retinal detachment.[3] We also showed a difference in VEGF concentrations between active proliferative DR (PDR) and quiescent DR, as well as before and after treatment with laser photocoagulation. Just 2 months prior to our publication, Dr. Adamis scooped us by publishing the presence of VEGF in 20 eyes of patients with diabetes.[4]

These findings opened the door to the general understanding that this protein is ubiquitous in many retinal vascular diseases.

PROS AND CONS

Since then, research into VEGF and potential inhibitors exploded, leading to the first FDA approval of an anti-VEGF agent, pegaptanib (Macugen, Eyetech Pharmaceuticals), in 2004. At the same time, bevacizumab and ranibizumab remained under study for cancer and AMD, respectively. Despite Genentech's contention that the large bevacizumab molecule couldn't penetrate the retina, in 2005, Philip J. Rosenfeld, MD, PhD, and Carmen A. Puliafito, MD, first used bevacizumab in patients and found impressive benefits. They

AT A GLANCE

- The therapeutic implications of anti-angiogenesis were first recognized in the 1970s for field of oncology.
- The development of anti-VEGF agents, with the first agent reaching ophthalmic clinical practice in 2004, has revolutionized the treatment paradigms for many retinal diseases.
- Innovations continue, with new agents, combinations of targets, and delivery methods in clinical trials.

shared this information and the details of compounding bevacizumab with me before their 2005 presentation at the American Society of Retina Specialists meeting. Our group put together a series of 79 AMD eyes,[5] which proved to be instrumental in obtaining insurance coverage for bevacizumab before ranibizumab was approved. In collaboration with Anat Loewenstein, MD, MHA, we evaluated bevacizumab toxicity in a rabbit model, using confocal microscopy to show that bevacizumab does, in fact, penetrate the retina.[6]

We helped pioneer the use of bevacizumab in PDR and diabetic macular edema (DME), first reporting the responses of patients with these indications.[5,7] We also noted fellow eye effects in PDR, prompting me to explore lower doses for this condition. Even when the dosage was reduced by a factor of 100 or 200, an effect on PDR neovascularization was seen.[5]

Based on these observations, I became interested in systemic safety, particularly in the treatment of ROP. When asked to comment on the observation of fellow eye effects in the pediatric population, I voiced my concerns in editorials in the *Journal of AAPOS*.[8,9] Bevacizumab has a serum half-life of 20 days compared with 2 hours for ranibizumab, raising concerns about systemic levels in babies with total blood volume 1/40th that of an adult. These infants are also in the process of organogenesis, and systemic suppression of VEGF could have detrimental effects on an infant's growth and development.[8] Current retrospective studies remain inconclusive, and the ROP population is difficult to study. But Wallace et al performed a dose de-escalation study in ROP down to 1/40th of an adult intravitreal dose of bevacizumab, and nine of nine patients had ROP resolution without recurrence—demonstrating that low doses can work.[10] Further study will determine if there is a significant safety concern.

2011 was a pivotal year, with the Comparison of Age-Related Macular Degeneration Treatments (CATT) trial results and aflibercept (Eylea, Regeneron) approval.[11] The CATT trial first showed comparable results for bevacizumab and ranibizumab for AMD and has provided numerous reports since. Aflibercept provided another agent with superior drying effects and has taken significant market share over the years.

WATCH IT NOW

Track the History—and Future—of Anti-VEGF Therapy

bit.ly/ARDSAVERY

NEXT WAVE

Conbercept (Chengdu Kanghong Biotech), an anti-VEGF agent approved in China since 2014, is making its way to the United States. The molecule is about the same size as aflibercept but reportedly has a higher binding affinity.[12] The company finished 36 months of follow-up in both of its pivotal studies, but there is concern that missed visits due to COVID-19 may impact the results.[13]

Kodiak is another company to watch; its drug candidate, KSI-301, is an anti-VEGF–biopolymer conjugate with a significantly longer half-life in the vitreous cavity than other anti-VEGF agents, given its molecular weight of almost 1 million daltons. The company is projecting an ocular equivalent concentration at 3 months postinjection of about 1,000-fold what would be expected of other agents—giving the potential for a sustained treatment effect for up to 6 months.[14]

Other pathways being investigated involve tyrosine kinase inhibitors (TKIs), with GB-102 (sunitinib malate, Graybug Vision) being the farthest along. Preliminary data from the company's phase 2b ALTISSIMO trial showed that median time to supportive therapy was 5 months; however, patients lost an average of 9 letters in that treatment arm.[15]

Ocular Therapeutix is developing a bioresorbable hydrogel implant that contains a TKI (OTX-TKI). Other formulations can also hold antibodies such as ranibizumab or aflibercept.[16] The implants are designed to deliver drugs for many months, potentially reducing the treatment burden.

Although nothing has been reported recently from PanOptica, the company has been working on a novel eye drop containing a TKI for the treatment of wet AMD. In a phase 1/2 trial, more than 50% of study participants receiving once-daily topical PAN-90806 ophthalmic suspension for 12 weeks did not need rescue with anti-VEGF intraocular injection at the study conclusion.[17]

We are also seeing developments in the anti-angiopoietin pathway. Roche/Genentech conducted global phase 3 clinical trials in wet AMD investigating faricimab, an antibody that binds to and inactivates angiopoietin-2 and VEGF-A. In two phase 3 trials in wet AMD, TENAYA and LUCERNE, approximately 50% of patients eligible for extended dosing were able to be treated every 4 months in the first year.[18]

The Port Delivery System (PDS, Roche) is moving through trials, and we will likely see it approved by the end of this year. In clinical trials, 98% of patients receiving the PDS filled with ranibizumab were able to go 6 months between refill injections.[19] Patients in the treatment group also maintained stable vision comparable with that in the monthly ranibizumab group.

Gene therapy is an exciting treatment possibility under investigation. In the phase 1 OPTIC trial, patients treated with ADVM-022 (Adverum Biotechnologies), an intravitreal injection gene therapy producing an aflibercept-like molecule, experienced an 85% reduction in annualized anti-VEGF injections, and two-thirds of patients did not require supplemental

AN OPHTHALMIC FORMULATION OF BEVACIZUMAB

An ophthalmic preparation of bevacizumab, bevacizumab-vikg (ONS-5010, Outlook Therapeutics), is moving through clinical trials. The drug is designed to address the potential complications of off-label use of repackaged bevacizumab (Avastin, Genetech), including the risks of inconsistent dosing, injection impurities, syringe concerns, and silicone oil bubble issues, according to Firas Rahhal, MD, a partner at Retina-Vitreous Associates Medical Group and Associate Clinical Professor of Ophthalmology at the UCLA School of Medicine.

In two registration trials, NORSE ONE and NORSE THREE, the new formulation showed a safety profile in line with published data for off-label use of bevacizumab, such as the 2011 CATT trials conducted by the US National Eye Institute. In press releases, the company said it expects efficacy and safety data from NORSE TWO, the ongoing pivotal trial of 228 patients being treated with bevacizumab-vikg monthly for 11 months, in the third quarter of 2021.[1,2]

Pending the results of these trials, the company hopes to have the data necessary to file a biologics license application under the PHSA 351(a) regulatory pathway, not as a biosimilar.[1] If approved, bevacizumab-vikg will be the first approved and cGMP-manufactured ophthalmic formulation of bevacizumab.

Pricing Considerations

The significant cost disparity between off-label repackaged bevacizumab and current FDA-approved anti-VEGF agents has many wondering how this new formulation will be priced. Larry Kenyon, Outlook's President, CEO, and CFO, said the price is expected to be closer to the current cost of off-label bevacizumab than that of the FDA-approved ophthalmic anti-VEGF options.

Future Indications

While Outlook Therapeutics moves forward with bevacizumab-vikg for treatment of wet AMD, it's already working with the FDA to start registration for clinical programs for bevacizumab-vikg indications for diabetic macular edema and branch retinal vein occlusion, according to the company.[1]

1. Outlook Therapeutics reports positive safety profile from Norse three open-label safety study for ONS-5010 / LYTENAVA (bevacizumab-vikg) [press release]. Outlook Therapeutics. March 31, 2021. https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeutics-reports-positive-safety-profile-norse-three. Accessed April 5, 2021
2. Outlook Therapeutics reports topline results and positive proof-of-concept for ONS-5010 / LYTENAVA (bevacizumab-vikg) from Norse 1 [press release]. Outlook Therapeutics. August 26, 2020. https://ir.outlooktherapeutics.com/news-releases/news-release-details/outlook-therapeutics-reports-topline-results-and-positive-proof. Accessed April 5, 2021

anti-VEGF injections with median follow up of 68 weeks.[20]

Subretinal delivery of RGX-314 (Regenxbio), an adeno-associated virus vector that encodes an anti-VEGF antibody extremely similar to ranibizumab, continues to look promising. In new interim data, a meaningful reduction in anti-VEGF treatment burden was seen in two of the trial's treatment cohorts (4 and 5) compared with the injection rate during the 12 months prior to RGX-314 administration.[21] In addition, suprachoroidal delivery is being tested in trials in AMD and DR.

FINAL THOUGHTS

The introduction of anti-VEGF therapy has had a greater effect on the world of retina than any other advance in the past few decades. It has changed our offices, our clinic flows, our pharmaceutical purchasing patterns, and myriad other aspects of our daily routines; but, most important, it has changed our patients' visual outcomes.

I was lucky enough to be an observer of, and sometimes a participant in, the development process. I'm fascinated by all of the innovations in the pipeline, and it will be interesting to see which ones will be the game-changers of the future. ■

1. Patz A. Retinal neovascularisation: early contributions of Professor Michaelson and recent observations. *Br J Ophthalmol*. 1984;68:42-46.
2. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285:1182-1186.
3. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331:1480-1487.
4. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol*. 1994;118(4):445-550.
5. Shahar J, Avery RL, Heilweil G, et al. Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina*. 2006;26:262-269.
6. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology*. 2006;113:363-372.
7. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina*. 2006;26(3):352-354.
8. Avery RL. Bevacizumab (Avastin) for retinopathy of prematurity: Wrong dose, wrong drug, or both? *J AAPOS*. 2012;16(1):2-4.
9. Avery RL. Extrapolating anti-vascular endothelial growth factor therapy into pediatric ophthalmology: promise and concern. *J AAPOS*. 2009;13(4):329-331.
10. Wallace DK, Kraker RT, Freedman SF, et al. Assessment of lower doses of intravitreous bevacizumab for retinopathy of prematurity: a phase 1 dosing study. *JAMA Ophthalmol*. 2017;135(6):654-656.
11. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011; 364:1897-1908.
12. Liu K, Song Y, Xu G, et al. Conbercept for treatment of neovascular age-related macular degeneration: Results of the randomized phase III PHOENIX study. *Am J Ophthalmol*. 2019;197:156-167.
13. Conbercept: New Generation of Product for Treatment of nAMD Completes 36-week Primary Endpoint Visits of Phase III Trial.[press release] December 23, 2020. Accessed April 1, 2021. www.prnewswire.com/news-releases/conbercept-new-generation-of-product-for-treatment-of-namd-completes-36-week-primary-endpoint-visits-of-phase-iii-trial-301197992.html
14. Kodiak. Our Pipeline. Accessed April 1, 2021. https://kodiak.com/our-pipeline
15. Graybug vision reports preliminary topline results from phase 2b ALTISSIMO trial [press release]. Graybug Vision. March 9, 2021. Accessed April 1, 2021. https://investors.graybug.vision/news-releases/news-release-details/graybug-vision-reports-preliminary-topline-results-phase-2b
16. Ocular Therapeutix. OTX-TKI. Accessed April 1, 2021. www.ocutx.com/research/otx-tki
17. PanOptica anti-VEGF eye drop shows promise in treatment of neovascular (wet) AMD [press release]. PanOptica. October 10, 2019. Accessed April 1, 2021. www.panopticapharma.com/wp-content/uploads/2019/10/PanOptica-PAN-90806-Data-Summary-Release-Clean-Final-Oct-09-2019.pdf
18. New phase III data show Roche's faricimab is the first investigational injectable eye medicine to extend time between treatments up to four months in two leading causes of vision loss, potentially reducing treatment burden for patients [press release]. Roche. February 12, 2021. Accessed April 1, 2021. www.roche.com/media/releases/med-cor-2021-02-12.htm
19. Phase III data show Roche's Port Delivery System with ranibizumab enabled over 98% of patients to go six months between treatments for neovascular age-related macular degeneration [press release]. Roche. July 22, 2020. Accessed April 1, 2021. www.roche.com/media/releases/med-cor-2020-07-22b.htm
20. Adverum Biotechnologies presents long-term data through March 10, 2021 from the OPTIC trial of ADVM-022 intravitreal gene therapy in Tteatment-experienced wet AMD patients at ARVO 2021 [press release]. Adverum Biotechnologies. May 1, 2021. Accessed May 17, 2021. https://investors.adverum.com/news-releases/news-release-details/adverum-biotechnologies-presents-long-term-data-through-march-10
21. Regenxbio announces additional positive interim phase I/IIa and long-term follow-up data of RGX-314 for the treatment of wet AMD [press release]. Regenxbio. February 16, 2021. Accessed April 1, 2021. https://regenxbio.gcs-web.com/news-releases/news-release-details/regenxbio-announces-additional-positive-interim-phase-iiia-and

ROBERT L. AVERY, MD

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

The Utility of CAM OCT Criteria for AMD Clinical Trials

Can this classification system help researchers consistently assess atrophy in patients undergoing treatment for AMD? New data suggest that it can.

AN INTERVIEW WITH GLENN J. JAFFE, MD

During the Classification of Atrophy Meetings (CAM) program, experts dug into the literature to review the OCT criteria researchers have been using to define macular atrophy—whether from wet or dry AMD, hereditary retinal degenerations, or other conditions. What came from those meetings was a classification system designed to help clinical researchers standardize the definitions of macular atrophy within their trials. Here, Glenn J. Jaffe, MD, shares his thoughts with *Retina Today* on using CAM OCT criteria in AMD clinical trials, and what future trials might look like.

RETINA TODAY: TELL US ABOUT THE CREATION OF THE CAM CRITERIA.

Glenn J. Jaffe, MD: The CAM criteria have been developed—primarily based on OCT findings with other supportive imaging modalities such as near-infrared reflectance and fluorescein angiography—specifically for macular atrophy.

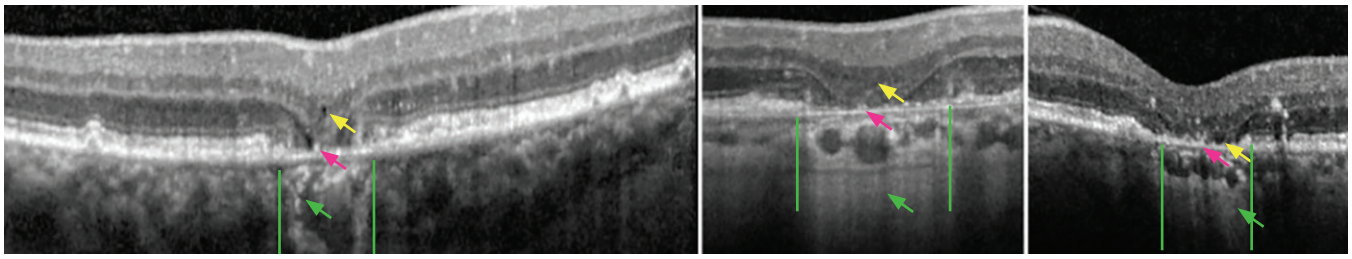
Macular atrophy is the general term used to describe atrophy that occurs in a variety of settings including AMD, hereditary retinal diseases, and others. *Geographic atrophy* (GA) is the specific term applied to macular atrophy that occurs in the setting of non-neovascular AMD. The CAM group defined atrophy according to an OCT-based classification. The OCT correlate of GA and macular atrophy that occurs in eyes with neovascular AMD is termed *complete retinal pigment epithelium (RPE) and outer retinal atrophy* (cRORA). To be classified as cRORA, an eye must show a triumvirate of signs: loss of outer retinal layers, RPE loss, and choroidal hypertransmission of at least 250 µm (Figure). In these eyes, the OCT signal penetrates more deeply into the choroid because the RPE, which normally forms a barrier, is lost, causing the choroidal hypertransmission.[1]

There is an earlier stage of atrophy, known as *incomplete RPE and outer retinal atrophy*, or iRORA. These eyes have similar characteristics, but they don't quite meet the full cRORA criteria. For example, there may be patchy loss of the RPE, less than 250 µm of RPE loss, or choroidal hypertransmission less than 250 µm.[2] iRORA, and the features that go along with it, will likely be important in many of the trials designed to prevent progression to cRORA. Right now, our treatments are focused on preventing growth of GA or cRORA, but there are also trials under way to investigate progression to iRORA, or from iRORA to cRORA.

We published a paper, CAM Report 5,[3] that describes the different features that accompany a higher risk of progression to cRORA, and many of those features are going to be used in upcoming clinical trials. More recently, in CAM Report 6, we determined the ability of readers from four reading centers to assess the different atrophy components, particularly those in the earlier atrophy stages.[4]

AT A GLANCE

- To be classified as complete retinal pigment epithelium (RPE) and outer retinal atrophy, there must be a loss of outer retinal layers, RPE loss, and choroidal hypertransmission of at least 250 µm.
- If the CAM criteria used in clinical trials are useful and reproducible, they would also be helpful when evaluating patients in the clinic.
- Loss of the outer retinal layers causes the inner retinal layers, including the inner nuclear layer and outer plexiform layer, to sink toward Bruch membrane, a feature termed *subsidence*, which is useful to help clinicians decide whether atrophy is present.



cRORA Features: Loss of the outer retina causes subsidence of the inner nuclear layer and outer plexiform layer. Loss of RPE. Choroidal hypertransmission.

RT: DO YOU SEE CAM CRITERIA BECOMING A STANDARD IN AMD TRIALS?

Dr. Jaffe: Clinicians have become increasingly aware of the CAM criteria. But the questions we sought to answer in a study presented at Angiogenesis, Exudation, and Degeneration 2021 was, "Should we be using CAM criteria in clinical trials to assess atrophy, and how well do they work?" We wanted to determine whether those criteria worked in real-world clinical trials. We did that by measuring how well two independent readers at the Duke Reading Center agreed with one another when they were grading the atrophy from clinical trials using CAM criteria—how well they could determine if the atrophy was gradable and, if it was, whether they could grade it reproducibly.

We then looked at whether it was useful to apply CAM criteria in terms of trial endpoints. For example, in macular atrophy trials comparing a drug treatment to placebo, or in trials in which macular atrophy is a safety endpoint, reproducibility must be good enough to separate the treatment group from the control group. Thus, we looked at the reproducibility of the CAM OCT assessments in a GA trial and in a trial of eyes with wet AMD. It turned out that the readers were able, with a high degree of reproducibility, to assess atrophy in both the GA trial and the wet AMD trial, and to make judgments about the atrophy in the different study groups.

RT: HOW MIGHT CAM CRITERIA TRANSLATE INTO CLINICAL PRACTICE?

Dr. Jaffe: Let's say you do a trial, and the treatment works for patients with atrophy. To decide whether a patient in your clinic might be a candidate for that treatment, you would need to know whether the patient really has atrophy. If the definitions used in the trial were useful and reproducible, they would also be helpful when evaluating patients in the clinic.

We have also been evaluating baseline features that accompany atrophy that might help us predict how a patient will fare with a given treatment. Would different atrophy patterns predict a different outcome? If they do, applying CAM criteria might be useful as a predictive tool. In addition, if CAM criteria help show that a patient has very little chance of success with the treatment based on their baseline criteria, a clinician might decide not to initiate a long-term treatment regimen.

More research into predictive factors based on CAM criteria could help us understand when one treatment works better than others—ultimately affecting a clinician's treatment approach. That will become increasingly important as we get more treatments for earlier stages of atrophy. CAM criteria will be quite valuable in the clinic once we have a drug that prevents progression to iRORA or a treatment that prevents conversion from iRORA to cRORA.

RT: HOW DO YOU SEE CAM CRITERIA EVOLVING OVER TIME?

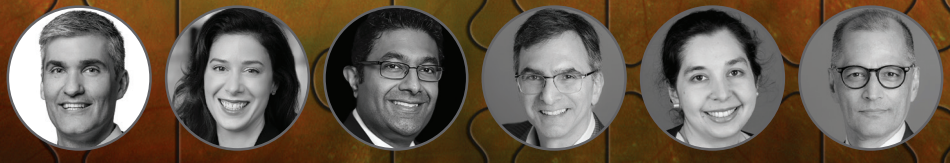
Dr. Jaffe: We came up with these definitions in the hopes that they would be practical. With further CAM consensus meetings, testing in the clinic, and feedback, we've been refining the criteria to make them more reproducible. For example, while choroidal hypertransmission is relatively easy to identify, RPE loss or attenuation can be challenging. With iRORA and cRORA, the retina looks like it sinks down, what we now call *subsidence*, a feature that can be determined reproducibly.[2] In addition, a hyporeflective wedge-shaped structure within Henle's fiber layer at the margins of the atrophy is another associated feature that can be determined reproducibly. Those features weren't emphasized in the earlier CAM criteria definitions, but we now know they are additional useful features that can help clinicians decide whether atrophy is present.

We're now focusing our efforts more on eyes with wet AMD and how to define the criteria. In general, it's more challenging to grade atrophy in eyes with wet AMD due to associated pathology, such as subretinal hyperreflective material, fibrosis, and intraretinal and subretinal fluid. Thus, we are directing more attention to defining the criteria a little better in those eyes. ■

1. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy report 3. *Ophthalmology*. 2018;125(4):537-548.
2. Guymer RH, Rosenfeld PJ, Curcio CA, et al. incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration: Classification of Atrophy Meeting Report 4. *Ophthalmology*. 2020;127(3):394-409.
3. Jaffe GJ, Chakravarthy U, Freund KB, et al. Imaging features associated with progression to geographic atrophy in age-related macular degeneration: Classification of Atrophy Meeting Report 5. *Ophthalmol Retina*. 2020 Dec 22;S2468-6530(20)30490-5.
4. Wu Z, Pfau M, Blodi BA, et al. Optical coherence tomography signs of early atrophy in age-related macular degeneration: inter-reader agreement. CAM Report 6. *Ophthalmol Retina*. Published online March 23, 2021. doi: 10.1016/j.oret.2021.03.008

GLENN J. JAFFE, MD
- Robert Machemer Professor of Ophthalmology; Chief, Vitreoretinal Division; Director, Duke Reading Center, Duke University, Durham, North Carolina
- Editorial Advisory Board Member, *Retina Today*
- glenn.jaffe@duke.edu
- Financial disclosure: Consultant (Iveric, Roche, Novartis, Gemini, EyePoint Pharmaceuticals)

Therapies on the Horizon for Nonexudative AMD



New targets in the complement pathway are showing promise for reducing geographic atrophy progression.

BY CHARLES C. WYKOFF, MD, PHD; ERIN HENRY, PHD; SRINIVAS R. SADDA, MD; JEFFREY S. HEIER, MD; NADIA K. WAHEED, MD, MPH; AND PRAVIN U. DUGEL, MD

A number of novel therapeutics targeting geographic atrophy (GA) progression are in the pipeline. Most of them focus on inhibiting the complement pathway or reversing the effects of oxidative stress. This article takes a look at the latest data and the next steps in the research.

NGM621

A novel monoclonal antibody inhibitor of complement C3 cleavage, NGM621 (NGM Biopharmaceuticals), is being developed as a potential treatment to reduce the progression of GA.

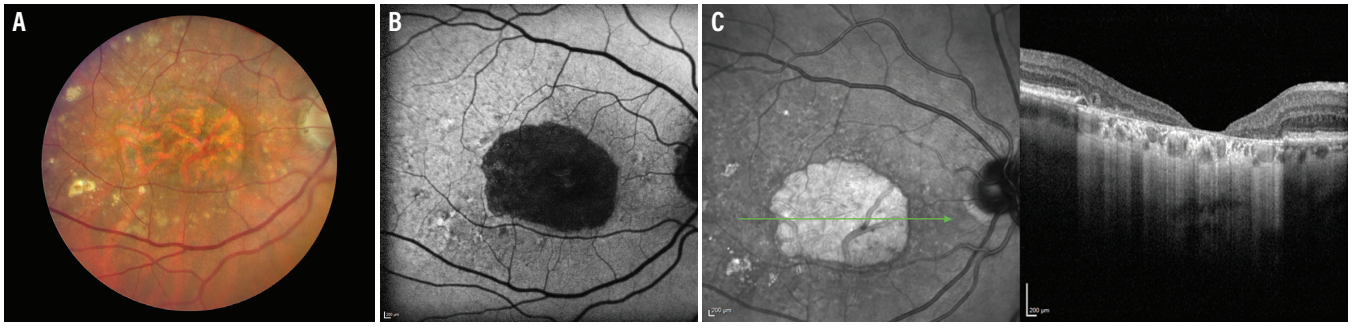
The objective of the phase 1 study, results of which were presented at Angiogenesis, Exudation, and Degeneration 2021, was to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of NGM621. In the study, 15 patients received NGM621 administered by intravitreal injection.[1] Study participants were 50 years of age or older with GA of 2.5 mm^2 or greater in at least one eye and BCVA between 54 and 4 letters in the study eye (Figure 1).

Four dosing cohorts were evaluated. In three single-dose cohorts, intravitreal NGM621 (2.0 mg, 7.5 mg, or 15.0 mg) was administered to three patients per dose; in a multidose cohort, patients received two 15.0 mg doses 4 weeks apart.

No drug-related adverse events, serious adverse events or deaths, endophthalmitis, intraocular inflammation, or new onset of choroidal neovascularization was observed. The 15.0-mg dose was well tolerated in both the single-dose and multidose cohorts. IOP was not meaningfully affected over time. Serum exposures of NGM621 appeared to be dose-proportional, with total NGM621 serum concentration

AT A GLANCE

- Two C3 inhibitors, NGM621 (NGM Biopharmaceuticals) and pegcetacoplan (Apellis Pharmaceuticals), and one C5 inhibitor, avacincaptad pegol (Zimura, Iveric Bio), are showing promise as potential treatments to reduce the progression of geographic atrophy.
- Elamipretide (Stealth Biotherapeutics) binds to cardiolipin to stabilize mitochondrial structure and reduce the emission of reactive oxygen species, thereby potentially slowing and reversing the effects of oxidative stress.
- A recombinant AAV2-based investigational gene therapy, GT005 (Gyroscope Therapeutics), is designed to induce the expression of complement factor I.



Images courtesy of Charles Wykoff, MD, PhD

Figure 1. Color fundus photography of the right eye shows signs of advanced GA (A). The corresponding autofluorescence in the same patient shows areas of RPE atrophy that are hypoautofluorescent (dark gray or black), areas of "sick" RPE that are hyperautofluorescent (brighter than background), and areas of healthy RPE that are gray (B). The corresponding near-infrared reflectance image in the same patient shows large choroidal vessels visible through the central area of GA; the green arrow shows complete atrophy of photoreceptors, RPE, and choriocapillaris, also shown in the B-scan on the right (C).

below that which would be expected to produce systemic complement inhibition. Additionally, all patiets were anti-drug antibody negative at all time points. As expected, GA lesion area and BCVA were generally stable over the 12-week study duration.

The results of this phase 1 dose-escalation study support the further development of NGM621 and indicate that doses of up to 15 mg are well tolerated and have a favorable pharmacokinetic/pharmacodynamic profile in patients with GA.

NGM621 is being further evaluated in the ongoing phase 2 CATALINA study, in which 15.0-mg doses are administered every 4 or 8 weeks compared with sham control.[2]

PEGCETACOPLAN AND NASCENT GA IN AMD

Pegcetacoplan (Apellis Pharmaceuticals) was recently shown to reduce the enlargement rate of GA lesions in AMD following intravitreal treatment monthly or every other month (29% and 20% reductions, respectively) in the phase 2 FILLY trial.[3] Two confirmatory phase 3 trials (DERBY[4] and OAKS[5]) are ongoing.

A post hoc analysis of the FILLY trial examined the impact of pegcetacoplan on nascent GA—a subset of eyes with incomplete retinal pigment epithelium (RPE) and outer retinal atrophy (iRORA) without choroidal neovascularization—and in particular on the progression of nascent GA outside of GA lesions (complete atrophy, known as cRORA).[6,7]

The analysis included individuals who completed 12 months of treatment from the monthly pegcetacoplan and sham arms and did not develop exudative AMD in the study eye. Regions on the OCT scans beyond 500 µm from the GA border at baseline and months 6 and 12 were evaluated for progression from iRORA to cRORA and progression from large drusen to iRORA and/or cRORA.

At baseline, iRORA was present in 45% and 52% of patients, and large drusen were present in 80% and 73% of patients in the monthly pegcetacoplan and sham groups, respectively. Progression from iRORA to cRORA at 12 months was 50.0% in the monthly pegcetacoplan group and 81.8% in the sham group (P = .02), indicating a 39% reduction in the rate of progression from iRORA to cRORA in patients treated with pegcetacoplan.

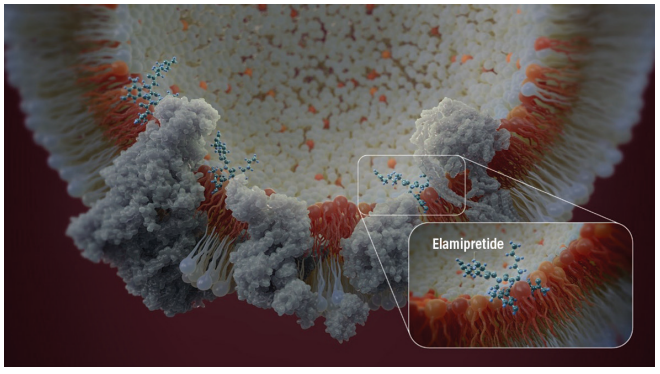


Image courtesy of Stealth Biotherapeutics

Figure 2. Elamipretide binds to cardiolipin in the mitochondrial membrane, as seen here, and restores mitochondrial structure and function.

At the lesion level, iRORA progression rates showed similar trends, with 37.9% and 64.3% in the monthly pegcetacoplan and sham groups, respectively.

Progression from large drusen to iRORA or cRORA at month 12 was 22.6% and 32.6% at the patient level (P = .34) and 9.2% and 11.8% at the lesion level in the monthly pegcetacoplan and sham groups, respectively.

Overall, these findings suggest that subjects receiving monthly intravitreal injections of pegcetacoplan have a lower rate of progression from nascent GA to GA compared with sham controls. The data seem to support further exploration of the potential of pegcetacoplan for earlier intervention in the course of GA.

ELAMIPRETIDE FOR NONCENTRAL GA

AMD is characterized by progressive mitochondrial dysfunction in RPE cells. Mitochondrial morphology is markedly disorganized in AMD RPE cells compared with normal eyes and is characterized by bleb formation on internal and external membranes.[8] Mitochondrial defects result in higher

reactive oxygen species levels, disrupting cristae curvature and the organization of respiratory complexes by damaging the cardiolipin protein complex, leading to cell death.

Elamipretide (Stealth Biotherapeutics) binds to cardiolipin to stabilize the mitochondrial structure and reduce emission of reactive oxygen species, thereby potentially slowing and reversing the effects of oxidative stress (Figure 2).

ReCLAIM was an open-label phase 1 clinical trial of subcutaneous elamipretide for the treatment of intermediate AMD. Individuals with noncentral GA and high-risk drusen were recruited. During the 24-week study, 40 patients received daily subcutaneous elamipretide 40 mg.[9]

Elamipretide was deemed safe and generally well tolerated, although injection site reactions were common. In the noncentral GA subgroup (n = 19), elamipretide-treated patients demonstrated statistically significant improvements in both BCVA and low-luminance visual acuity (LLVA): 4.6 ± 5.1 (P = .003) and 5.4 ± 7.9 (P = .019) letters, respectively.

By the 24-week visit, LLVA had improved by more than 5 letters in 53.3% of patients, more than 10 letters in 33.3% of patients, and more than 15 letters in 6.7% of patients. Although a minimal difference in mean best-corrected reading acuity was seen between the two groups, low-luminance reading acuity through a log-2 neutral density filter improved by an average of -0.52 ± 0.75 logMAR (P < .017) compared with baseline values.

The developers felt that these results supported the initiation of ReCLAIM-2, a phase 2 randomized, placebo-controlled clinical trial of subcutaneous elamipretide in patients with noncentral GA with a primary endpoint of LLVA at 48 weeks.[10]

GT005 GENE THERAPY FOR THE TREATMENT OF GA

Histopathologic and genome-wide association studies point to complement system overactivation as a driver of disease in AMD. However, the body has an intrinsic down-regulator of the alternative pathway, complement factor I (CFI).[11,12] A recombinant AAV2-based investigational gene therapy administered subretinally, GT005 (Gyroscope Therapeutics), is designed to induce expression of CFI.

FOCUS is a phase 1/2 open-label study evaluating the safety and tolerability of GT005 in patients with GA secondary to AMD.[13] Cohorts 1 through 3 are dose-escalation cohorts for which enrollment is complete. Cohort 4 is a dose-expansion cohort for which enrollment is ongoing.

In interim results from cohorts 1 through 4, presented at Angiogenesis, Exudation, and Degeneration 2021, the three dose levels of GT005 were well-tolerated in 19 patients. No serious adverse events related to GT005 and no safety signal on laboratory parameters were observed. Most surgery-related adverse events were mild. Vitreous sampling showed that, in the 12 to 48 weeks after administration of GT005, nine of 10 patients treated with GT005 had increases in vitreous CFI levels, with an average increase of 146% compared with baseline. Down-regulation of complement activation was also observed downstream from CFI: treatment with GT005 led to a sustained decrease in both local Ba and C3 breakdown products

DISRUPTING THE C3 PATHWAY

BY CEDRIC FRANCOIS, MD, PHD

C3, a protein that circulates throughout the body in high concentrations, naturally reacts covalently with all cell surfaces in the body.

Think of C3 as a graffiti artist continuously painting all of the cells in the body, indiscriminately. As we age, the graffiti-like painting of C3 gets heavier, while the body becomes less able to clear it effectively.

The mechanisms required to clear an overabundance of C3 are the same as those required for the visual cycle in the retina. Thus, excess C3 forces cells to choose between clearing C3 and maintaining the visual system. The eventual disruption in visual processes (the earliest sign's being dark adaptation issues) is followed by destruction of retinal cells—like a wildfire in the retina.

To arrest this process, there must be sufficient control of complement to allow cells to remove more C3 than what accumulates. Pegcetacoplan (Apellis Pharmaceuticals), a C3 inhibitor, is showing promise in targeting this complement pathway.

Several specifics of a post-hoc analysis of the FILLY trial support the investigational treatment's efficacy. For one, the researchers halted treatment at 12 months to correct for covert behavior, ensuring that the lower progression rate seen in the patients treated with pegcetacoplan was not simply a differing rate of progression at baseline.

The analysis also looked at patients with bilateral GA and compared the treated eye with the contralateral eye. The data showed a trend with treatment every other month and a statistically significant reduction in the monthly dosing group in the treated eye compared with the contralateral eye. Using the contralateral eyes as controls reinforced the increased effect of treatment over time in the pegcetacoplan group.

CEDRIC FRANCOIS, MD, PHD

- Co-Founder and Chief Executive Officer, Apellis Pharmaceuticals, Waltham, Massachusetts
- Financial disclosure: Employee (Apellis Pharmaceuticals)

in the range of 41% to 42% at the 24- to 56-week timepoints, and there appeared to be a linear correlation between the increase in CFI levels and the decrease in Ba. Phase 2 trials to further evaluate the potential to slow the progression of GA secondary to AMD are ongoing.

C5 INHIBITION FOR THE TREATMENT OF GA

Avacincaptad pegol (Zimura, Iveric Bio), a complement C5 inhibitor, reduced the progression of GA secondary to AMD by approximately 28% compared with sham control in 18-month follow-up of the GATHER 1 phase 3 clinical trial.[12,14] This is the only positive pivotal trial with continuous treatment for 18 months in GA. The study met its pre-specified primary endpoint and demonstrated a best-in-class safety profile.

A total of 286 patients were enrolled in the trial. Those in the treatment arm were dosed with either 2 mg or 4 mg avacincaptad pegol. Of those treated with the 2-mg dose, 92.5% had nonsubfoveal GA, as did 97.6% of those treated with the 4-mg dose. The data showed a statistically significant 28.11% reduction in the mean rate of GA growth (P = .0014) for the 2-mg group compared with the control group and 29.97% for the 4-mg group (P = .0021).

After 18 months of administration, avacincaptad pegol was generally well tolerated with no discontinuations or adverse events related to the study drug.

The company has initiated a second phase 3 clinical trial, GATHER 2, and is enrolling approximately 400 patients who will be randomly assigned to receive either monthly administration of avacincaptad pegol 2 mg or sham. Upon achieving the prespecified primary endpoint at month 12, Iveric Bio will file for approval of Zimura in GA. ■

1. Study of NGM621 in Participants With Geographic Atrophy. Accessed April 12, 2021. clinicaltrials.gov/ct2/show/NCT04014777
2. A study of NGM621 in participants with geographic atrophy (CATALINA). Accessed April 21, 2021. clinicaltrials.gov/ct2/show/NCT04465955
3. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127(2):186-195.
4. Study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy (GA) secondary to age-related macular degeneration. Accessed April 6, 2021. clinicaltrials.gov/ct2/show/NCT03525600
5. A study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy (GA) secondary to age-related macular degeneration. Accessed April 6, 2021. clinicaltrials.gov/ct2/show/NCT03525613
6. Corradetti G, Corvi F, Nittala MG, et al. Natural history of incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration. Published online February 1, 2021. *Can J Ophthalmol*. doi:10.1016/j.jcjo.2021.01.005
7. Guymer RH, Rosenfeld PJ, Curcio CA, et al. Incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration: classification of atrophy meeting report 4. *Ophthalmology*. 2020;127(3):394-409.
8. Feher J, Kovacs I, Artico M, Cavallotti C, Papale A, Balacco Gabrieli C. Mitochondrial alterations of retinal pigment epithelium in age-related macular degeneration. *Neurobiol Aging*. 2006;27(7):983-993.
9. ReCLAIM-2 study to evaluate safety, efficacy & pharmacokinetics of elamipretide in subjects with AMD with non-central GA (ReCLAIM-2). Accessed April 12, 2021. clinicaltrials.gov/ct2/show/NCT03891875
10. Csaky K, Ferris F 3rd, Chew EY, et al. Report from the NEI/FDA endpoints workshop on age-related macular degeneration and inherited retinal diseases. *Invest Ophthalmol Vis Sci*. 2017;58(9):3456-3463.
11. Liao DS, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127(2):186-195.
12. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128(4):576-586.
13. Waheed N. FOCUS interim results: GT005 gene therapy phase I/II study for the treatment of geographic atrophy. Presented at: Angiogenesis, Exudation, and Degeneration 2021; February 12, 2021.
14. Iveric Bio announces positive Zimura 18 month data supporting the 12 month efficacy findings: continuous positive treatment effect with favorable safety profile in geographic atrophy secondary to age-related macular degeneration in a phase 3 trial [press release]. Iveric Bio. June 15, 2020. Accessed April 12, 2021. https://investors.ivericbio.com/news-releases/news-release-details/iveric-bio-announces-positive-zimura-18-month-data-supporting-12

PRAVIN U. DUGEL, MD
- Executive Vice President, Chief Business and Strategy Officer, Iveric Bio, New York, New York
- Editorial Advisory Board Member, *Retina Today*
- pdugel@gmail.com
- Financial disclosure: Consultant (Acucela, Aerpio, Alcon, Bausch + Lomb, Genentech, Graybug Vision, Novartis, Ophthotech, Opthea, Oxurion, PanOptica, Regeneron); Minor Stockholder (Aerpio, Ophthotech); Scientific Advisory Board (Genentech, Graybug Vision, Novartis)

JEFFREY S. HEIER, MD
- Director of Retina Service & Director of Retina Research, Ophthalmic Consultants of Boston
- Editorial Advisory Board Member, *Retina Today*
- jsheier@eyeboston.com
- Financial disclosure: Consultant (4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Aviceda, BVT, Dark Horse, DTx, Eloxx, Galimedix, Genentech, Graybug, Gyroscope, Iveric Bio, jCyte, Kanghong, LensGen, NGM, Novartis, Ocular Therapeutix, OcuTerra, Oxurion, Palatin, Regeneron, Regenxbio, Stealth, Thea, Verseon, Vinci, Voyant); Research Grants (Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hemera, Iveric Bio, Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, Stealth)

ERIN HENRY, PHD
- Executive Director, Ophthalmology Clinical Development, NGM Biopharmaceuticals, South San Francisco, California
- ehenry@ngmbio.com
- Financial disclosure: Employee (NGM)

SRINIVAS R. SADDA, MD
- Director, Artificial Intelligence and Imaging Research, Doheny Eye Institute, Los Angeles
- Professor of Ophthalmology, David Geffen School of Medicine, University of California, Los Angeles
- ssadda@doheny.org
- Financial disclosure: Consultant (Amgen, Allergan, Apellis, Centervue, 4DMT, Heidelberg, Iveric Bio, Merck, Novartis, Optos, Roche/Genentech)

NADIA K. WAHEED, MD, MPH
- Associate Professor, Tufts University School of Medicine, Boston
- Chief Medical Officer, Gyroscope Therapeutics
- nadiakwaheed@gmail.com
- Financial disclosure: Employee (Gyroscope)

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

GLAUCOMA IN THE RETINA PRACTICE: PART 2


Understanding the mechanism of IOP elevation after vitreoretinal surgery helps guide the best management approach.

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

Elevated IOP is not uncommon after pars plana vitrectomy (PPV), especially in complex cases. Many causes exist, the most common of which are gas mixture– or silicone oil–related IOP elevation, particulate glaucomas, trabeculitis, viscosity glaucoma, and steroid-induced glaucoma. Management varies depending on the underlying etiology.

In Part 1 of this series, we reviewed the management of primary open-angle glaucoma in the retina practice. In this article, we explore the mechanisms of postoperative glaucomas and optimal management approaches.

CAUSES OF POSTOPERATIVE IOP ELEVATION

Perioperative Gas-Related

Elevated IOP in gas-filled eyes after PPV is almost always iatrogenic. The cause is inadvertent or intentional use of a gas concentration greater than the isoexpansive concentration of the gas (25% for SF_6 or 18% for C_3F_8).[1] A common mistake is to record the number of cubic centimeters of gas on the surgeon's preference card or electronic protocol system but fail to calculate the correct gas concentration when a syringe smaller than the usual 60 cubic centimeters is used.

Some surgeons believe that the presence of severe proliferative vitreoretinopathy demands the use of a higher gas concentration. However, no rationale supports this belief. Some surgeons perform total fluid-air exchange followed by estimating the volume of the vitreous cavity (a practice fraught with error) and then injecting 100% SF_6 or C_3F_8. This approach can produce a significantly greater than isoexpansive concentration and high IOP or, conversely, a low gas concentration resulting in a small ineffective gas bubble.

A critical error is caused by prescribing prn pain medications for 1 or more days after surgery using gas. In instances when a gas mixing error is made, the patient calls at night reporting pain, for which the on-call ophthalmologist prescribes medication. However, the pain is secondary to elevated IOP, not to the surgery per se.

In this scenario, the patient takes oral pain medication, which masks the pain. Subsequently, the patient is examined in the office and has no light perception or hand motion vision and a central retinal artery occlusion and/or optic nerve ischemia. This is more likely in vit-buckle patients because they have more postoperative pain, making assessment by the patient or on-call ophthalmologist more challenging.

Intraoperative Silicone Oil-Related

Air–silicone oil exchange can cause overpressurization if one cannula is removed and silicone oil is injected, forcing air back into the console air source. Instead, surgeons should vent the nasal sclerotomy with the supplied vent to hold the valve open. The fill is complete when oil comes out of the vent with the eye rotated and the vent higher than the silicone oil injection cannula.

Injecting too much oil and not checking tactile IOP is another common mistake; oil is incompressible. Glaucoma medications cannot lower IOP that is too high due to the presence of too much silicone oil.

Oil-induced pupillary block in aphakic eyes occurs when the capsule is not completely removed in lensectomy or extracapsular cataract extraction surgery. Capsular fibrosis virtually always closes the inferior peripheral iridectomy needed to enable aqueous to enter the anterior chamber to prevent pupillary block. In these types of lens surgeries, there is no merit to leaving the capsule for subsequent sulcus IOL implantation because it results in epiciliary tissue, hypotony, concave iris, and iridectomy closure via fibrosis.[2,3] The presence of iridocapsular adhesions makes subsequent sulcus implantation of an IOL rarely possible.

Particulate Glaucomas

There are several causes of the *particulate glaucomas*, a term coined by one of us (S.C.). One common etiology is silicone oil emulsification (Figure 1). Silicone oil droplets never

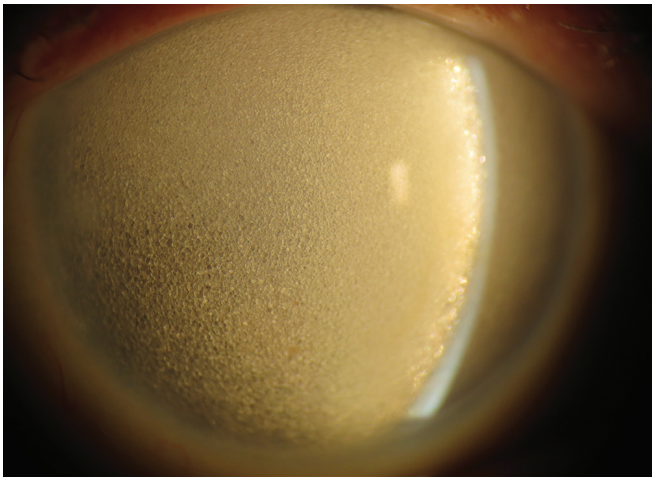


Figure 1. Diffuse silicone oil emulsification in the anterior chamber.

absorb; instead, they become embedded in the trabecular meshwork, impeding aqueous outflow, and they often become trapped in the zonules, residual peripheral vitreous, epiretinal membranes, and capsular bag.[4]

Inflammation reduces interfacial surface tension, causing increased emulsification; thus, many patients require topical steroids for as long as the oil is in the eye. However, long-term topical steroids can induce glaucoma and exacerbate herpes simplex keratitis and other corneal disorders.

Bleeding also reduces interfacial surface tension; hemostasis is crucial in cases with oil but is virtually impossible in diabetic traction retinal detachment cases. An ophthalmic viscoelastic device reduces interfacial surface tension, but viscodissection has fortunately been largely abandoned.[5,6] Incomplete silicone oil fill increases the shear angle, thereby increasing emulsification.

Another type of particulate glaucoma, perfluorocarbon liquid (PFCL) droplet-related glaucoma, occurs if medium-term removal of perfluoro-n-octane is inadequate after its use for inferior retinal detachment or nasal, temporal, and inferior giant retinal breaks.[7,8] PFCL often becomes trapped in the zonules, residual peripheral vitreous, epiretinal membranes, and capsular bag (Figure 2).

Retained lens particles can become embedded in the trabecular meshwork after lensectomy or complicated phacoemulsification, resulting in particulate glaucoma.[9]

Finally, erythroclasts (ghost cells) cause particulate glaucoma. This is a good reason to remove as much peripheral vitreous as possible during surgery for dense vitreous hemorrhage, without damaging the peripheral retina or the lens.[10]

Viscosity Glaucoma

Elevated IOP caused by high protein content in the anterior chamber is known as *viscosity glaucoma*, another term coined by one of us (S.C.). Increased aqueous humor viscosity is caused by inflammation, anterior segment neovascularization, and retained viscoelastic substances after combined phacoemulsification-vitrectomy.

Inflammation can be caused by iris manipulation, mechanical pupillary dilation, and iris hooks during this type of surgery. Inflammation causes trabeculitis as well, which also reduces outflow.

Use of an ophthalmic viscoelastic device in the anterior chamber is an excellent way to keep silicone oil or gas bubbles out of the anterior chamber in phakic or pseudophakic eyes during vitreoretinal surgery.

Steroid-Induced Glaucoma

This form of glaucoma is delayed days to weeks after vitrectomy. Subconjunctival triamcinolone is more likely to cause elevated IOP than dexamethasone because the duration of the former is greater. Topical difluprednate is associated with a higher rate of steroid-induced glaucoma than prednisolone, but for a 2-week postoperative period it is ideal, unless the patient is a known steroid responder.[11]

Intravitreal injection of triamcinolone is an excellent technique to enhance vitreous visualization, but care should be taken to remove as much as possible during the vitrectomy.

The dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) should be used with caution in pseudophakic post-PPV eyes and never used in aphakic post-PPV eyes. Injection of the implant in this setting increases the risk of its migration to the anterior chamber, resulting in rapid corneal endothelial damage.[12] It is crucial to keep in mind that all patients are steroid responders if the dose is high enough.

Pupillary Block Glaucoma

Aphakic patients managed with iso-expansive gas tamponade must be instructed not to sleep in the supine position to prevent pupillary block glaucoma. Proper positoning is the best approach to manage this complication.

MANAGEMENT APPROACHES

Perioperative Silicone Oil- or Gas-Related

Pars plana tap is the best option to manage perioperative high IOP caused by an excessive oil or gas bubble or higher IOP elevation caused by gas expansion. A 30-gauge needle is ideal for gas, whereas a 23- to 25-gauge needle or cannula inserted with a trocar is required for removal of silicone oil.

Anterior chamber paracentesis causes oil or gas to migrate into the anterior chamber of pseudophakic or aphakic eyes. Medical management in these cases is ineffective.

Particulate Glaucomas

Small lens particles will absorb, but larger amounts must be removed via vitrectomy. A lens nucleus virtually always must be removed because it engenders an inflammatory response. If you choose to conservatively manage nuclear material in the vitreous cavity after complicated cataract surgery, a frosted appearance on the surface of the material is

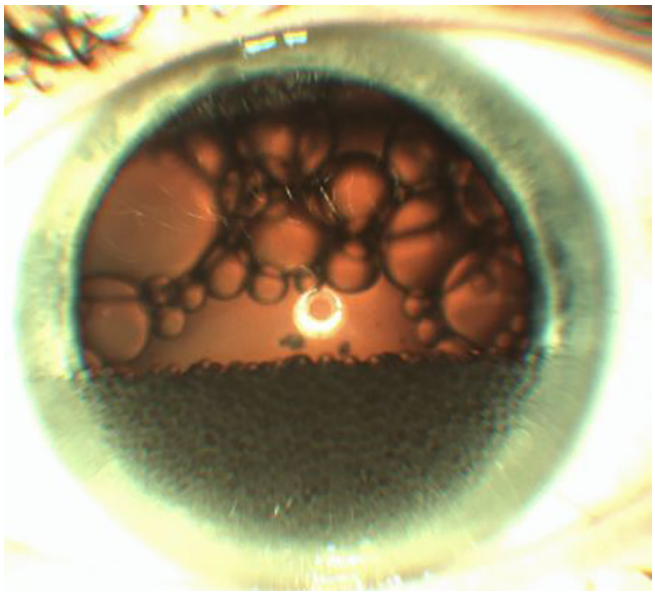


Figure 2. PFCL droplets in the inferior anterior chamber and posterior to the lens before intraoperative removal of medium-term perfluoro-n-octane.

caused by macrophages—an indication for removal.

Because retained PFCL droplets and silicone oil emulsification never absorb, one of us (S.C.) has developed two office-based methods to manage the resultant elevated IOP.[4,8]

In these techniques, one needle is used to infuse balanced salt solution, and a second is used for droplet egress. This is effective for removal of material from the anterior chamber. The procedure must be performed with the patient supine using an operating microscope or loupes for silicone oil. For PFCL droplet removal, the procedure must be performed while seated at the slit lamp.

In either instance, a tuberculin syringe open to the atmosphere is used as a handle for the egress needle. The balanced salt solution injection needle is connected via a short segment of sterile tubing to a syringe operated by an assistant. The egress needle tip for PFCL removal from the anterior chamber must be bevel up, inserted exactly at the 6 clock position. The needle tip for silicone oil removal must be near the corneal endothelium at the center of the cornea, hence the need for an operating microscope (preferred) or loupes.

Vitrectomy revision and repeated fluid-air exchange using a backflush cannula at the oil-air interface is required for the removal of silicone oil emulsification from the vitreous cavity.

A tube shunt must be placed inferiorly in an oil-filled eye, and the patient should be instructed to avoid supine ocular massage to keep oil from migrating into the tube shunt.

In the particulate glaucomas, medications that reduce aqueous production are more effective than topical agents that increase outflow. If endocyclophotocoagulation is performed, use of a 25-gauge articulated, illuminated probe is better than use of a conventional large-diameter nonarticulated endocyclophotocoagulation device.

Viscosity Glaucoma

Anterior segment neovascularization results in higher viscosity of the aqueous humor; anti-VEGF agents injected into the vitreous cavity or anterior chamber can reduce viscosity and thereby IOP.[13] Topical, subconjunctival, or intravitreal steroid injection can also reduce inflammation (flare), aqueous viscosity, and IOP.

Often a short course of topical glaucoma medications is needed in addition to the steroid or anti-VEGF agent until inflammation and/or anterior chamber protein levels are sufficiently reduced.

Repeated paracentesis immediately reduces IOP in viscosity glaucoma as well as particulate glaucomas.

UNDERSTAND THE MECHANISM

A variety of mechanisms can cause elevated IOP after PPV. Understanding them drives selection of optimal treatment strategies. Pars plana tap and paracentesis are excellent but underutilized tools. Office-based removal of retained PFCL droplets and silicone oil emulsification in eyes after oil removal or in phakic or pseudophakic eyes are relatively new techniques that can be very effective. ■

1. Chen PP, Thompson JT. Risk factors for elevated intraocular pressure after the use of intraocular gases in vitreoretinal surgery. *Ophthalmic Surg Lasers*. 1997;28(1):37-42.
2. Jonas JB, Knorr HL, Rank RM, Budde WM. Intraocular pressure and silicone oil endotamponade. *J Glaucoma*. 2001;10(2):102-108.
3. O'Connell SR, Majji AB, Humayun MS, de Juan E Jr. The surgical management of hypotony. *Ophthalmology*. 2000;107(2):318-323.
4. Al-Jazzaf AM, Netland PA, Charles S. Incidence and management of elevated intraocular pressure after silicone oil injection. *J Glaucoma*. 2005;14(1):40-46.
5. Costagliola C, Semeraro F, dell'Omo R, et al. Some physicochemical remarks on spontaneous emulsification of vitreal tamponades. *Biomed Res Int*. 2014;2014:243056.
6. Charles S, Calzada J, Wood B. General posterior segment techniques. In: *Vitreous Microsurgery*. 5th ed. Lippincott Williams & Wilkins; 2011:53-54.
7. Sigler EJ, Randolph JC, Calzada JI, Charles S. Pars plana vitrectomy with medium-term postoperative perfluoro-N-octane for recurrent inferior retinal detachment complicated by advanced proliferative vitreoretinopathy. *Retina*. 2013;33(4):791-797.
8. Sigler EJ, Randolph JC, Calzada JI, Charles S. 25-gauge pars plana vitrectomy with medium-term postoperative perfluoro-n-octane tamponade for inferior retinal detachment. *Ophthalmic Surg Lasers Imaging Retina*. 2013;44(1):34-40.
9. Epstein DL. Diagnosis and management of lens-induced glaucoma. *Ophthalmology*. 1982;89(3):227-230.
10. Han DP, Lewis H, Lambrou FH Jr, Mieler WF, Hartz A. Mechanisms of intraocular pressure elevation after pars plana vitrectomy. *Ophthalmology*. 1989;96(9):1357-1362.
11. Jeng KW, Fine HF, Wheatley HM, Roth D, Connors DB, Prenner JL. Incidence of steroid-induced ocular hypertension after vitreoretinal surgery with difluprednate versus prednisolone acetate. *Retina*. 2014;34(10):1990-1996.
12. Khurana RN, Appa SN, McCannel CA, et al. Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. *Ophthalmology*. 2014;121(1):67-71.
13. Zhou M, Chen S, Wang W, et al. Levels of erythropoietin and vascular endothelial growth factor in surgery-required advanced neovascular glaucoma eyes before and after intravitreal injection of bevacizumab. *Invest Ophthalmol Vis Sci*. 2013;54(6):3874-3879.

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

ADAM PFLUGRATH, MD
- Vitreoretinal Surgery Fellow, Charles Retina Institute, Germantown, Tennessee
- apflugrath@charlesretina.com
- Financial disclosure: None

INTRAARTERIAL CHEMOTHERAPY: THE LATEST TIDAL WAVE

Here's a look at the evolution of this therapeutic option for the management of retinoblastoma.

BY ZAYNAB SAJJADI, BA; ANTONIO YAGHY, MD; FAIROOZ P. MANJANDAVIDA, MD; AND CAROL L. SHIELDS, MD

The landscape of retinoblastoma management has changed significantly since the initial earthquake caused by the introduction of intravenous chemotherapy (IVC) in the early 1990s, followed by the tidal wave of intraarterial chemotherapy (IAC) in 2006, and finally the tsunami of intravitreal chemotherapy in 2012.[1-3] In this review, we focus on IAC, which dramatically improved unilateral and bilateral retinoblastoma management.[4]

IAC allows direct delivery of chemotherapy to the affected eye through the ophthalmic artery. In recent years, this technique has gained tremendous popularity as both a primary treatment for newly diagnosed retinoblastoma and as a secondary treatment for recurrent retinoblastoma, owing to its proven efficacy for tumor control.[4,5]

RELIABLE CLASSIFICATION

The International Classification of Retinoblastoma (ICRB) was created in 2003 to predict treatment outcomes with IVC methods, replacing the older Reese-Ellsworth classification that focused on control after external beam radiotherapy (EBRT). The ICRB accounts for tumor size and location, as well as other factors such as subretinal and vitreous seeding (Table 1). In 2006, Shields et al demonstrated that ICRB was reliable in predicting globe salvage after IVC.[6] The team found that IVC led to globe salvage and avoidance of EBRT in 100% of eyes in Group A, 93% of eyes in Group B, 90% of eyes in Group C, and 47% of eyes in Group D. Group E eyes were treated with enucleation.[6]

A more recent long-term study revealed that IVC treatment (with additional IAC or plaque radiotherapy) for patients with retinoblastoma provided tumor control at 20 years in 96% of Group A, 90% of Group B, 90% of Group C, 68% of Group D, and 32% of Group E eyes.[7]

TREATMENT ADVANCES

IAC is a remarkably successful therapy whereby a catheter is inserted into the ipsilateral femoral artery and guided into the aorta, the carotid artery, and the internal carotid artery, finally peeking into the orifice of the ophthalmic artery.[4] In

TABLE 1. INTERNATIONAL CLASSIFICATION OF RETINOBLASTOMA (ICRB)

Group	Mnemonic	Features
A	Sm**A**ll tumor	Retinoblastoma ≤ 3 mm in basal diameter or thickness
B	**B**igger tumor beside macula or optic nerve	Retinoblastoma > 3 mm in basal diameter or thickness *or* Macular location (≤ 3 mm from foveola) *or* Juxtapapillary location (≤ 1.5 mm to disc) *or* Subretinal fluid (≤ 3 mm from margin)
C	**C**ontiguous seeds	Retinoblastoma with: Subretinal seeds ≤ 3mm from tumor *or* Vitreous seeds ≤ 3 mm from tumor *or* Both
D	**D**iffuse seeds	Retinoblastoma with: Subretinal seeds > 3 mm from tumor *or* Vitreous seeds > 3 mm from tumor *or* Both
E	**E**xtensive tumor	Retinoblastoma occupying > 50% of globe *or* Neovascular glaucoma *or* Opaque media from hemorrhage *or* Invasion of optic nerve, choroid, sclera, orbit, anterior chamber

Adapted from: Shields CL, Shields JA. Basic understanding of current classification and management of retinoblastoma. *Curr Opin Ophthalmol*. 2006;17:228-234.

TABLE 2. GLOBE SALVAGE BY ICRB GROUP IN PATIENTS TREATED WITH IAC

Authors (number of eyes)	Year	Globe salvage rate by groups (%)				
		A	B	C	D	E
Suzuki et al (408)	2011	100	88	65	45	30
Thampi et al (20)	2013	100	100	100	50	33
Parareda et al (12)	2014	na	100	100	50	na
Ghassemi et al (24)	2014	na	100	0	72	66
Shields et al (70)	2014	na	100	100	94	36
Ong et al (17)	2015	na	67	100	100	57
Leal-Leal et al (12)	2016	na	50	100	30	na
Tuncer et al (24)	2016	na	na	na	67	na
Abramson et al (120)	2016	100	100	100	100	90
Munier et al (25)	2017	na	na	na	100	na
Chen et al (107)	2017	na	100	100	78.5	62
Ammanuel et al (43)	2018	0	90	64	69	50
Ronjanaporn et al (27)	2019	na	100	100	75	9
Shields et al (341)*	2021	na	100	100	86	55

Adapted from: Manjandavida FP, Stathopoulos C, Zhang J, Honavar SG, Shields CL. Intra-arterial chemotherapy in retinoblastoma - A paradigm change [published correction appears in *Indian J Ophthalmol*. 2019;67(8):1385]. *Indian J Ophthalmol*. 2019;67(6):740-754.
*Adapted from: Shields CL, Dockery PW, Yaghy A, et al. Intra-arterial chemotherapy for retinoblastoma in 341 consecutive eyes (1292 infusions): Comparative analysis of outcomes based on patient age, race, and sex. *J AAPOS*. 2021 [In press].

TABLE 3. FIVE-YEAR GLOBE SALVAGE RATES IN 341 EYES TREATED WITH IAC

Variable	Globe salvage rate at 5 years (%)
IAC overall	
All patients	74%
IAC based on treatment	
As primary treatment	76%
As secondary treatment	71%
IAC for tumor recurrence	
If solid tumor recurrence	80%
If subretinal seeds recurrence	60%
If vitreous seeds recurrence	88%
IAC based on patient age	
If 0-12 months	77%
If > 12 months	72%
P value	< .001

Adapted from: Shields CL, Dockery PW, Yaghy A, et al. Intra-arterial chemotherapy for retinoblastoma in 341 consecutive eyes (1292 infusions): Comparative analysis of outcomes based on patient age, race, and sex. *J AAPOS*. 2021 [In press].

an early study of 70 eyes, IAC as primary therapy without radiotherapy led to tumor control and globe salvage in 72% of eyes; as secondary therapy, it was successful in 62%.[8]

Other studies have demonstrated improved rates of globe salvage with IAC (Table 2).[4] Assessing IAC per ICRB classification, success with tumor control and globe salvage without radiotherapy was 100% in Groups B and C, 94% in Group D, and 36% in Group E eyes.[8] For unilateral retinoblastoma, Shields et al found that IAC had special benefit in Group D eyes, with improved globe salvage of 91% compared with 48% with IVC ($P = .004$).[9] Munier et al showed comparable results for Group D eyes treated with IAC, with globe salvage in 100% compared with 57% in those treated with IVC ($P < .001$).[10]

IAC is both safe and effective when performed at an experienced center. An international analysis of 1,139 patients treated with 4,396 IAC infusions at six experienced centers in the United States, Europe, and Latin America reported a less than 1% risk for metastatic death.[2] All deaths from metastasis occurred in Latin America from poor patient follow-up or family refusal of enucleation.[2] Our team specifically evaluated IAC-induced vascular complications at a single center in the early IAC era (2009–2011) compared with the recent era (2012–2017) and found decreased complications over time and no vascular events in eyes treated in 2016 or 2017.[11]

THE LATEST DATA

In a recent report, Shields et al evaluated outcomes of primary and secondary IAC based on patient age, race, and sex in a cohort of 341 consecutive eyes with retinoblastoma that underwent 1,292 infusions from 2008 to 2020 at a single center.[12] Kaplan-Meier analysis revealed impressive 5-year globe salvage rates of 74% in the entire cohort, 76% in patients treated with IAC as primary therapy, and 71% in those treated with IAC as secondary therapy (Table 3). Without IAC, many of these eyes would likely have undergone enucleation.

The 5-year globe salvage rates with IAC as secondary therapy differed by the type of recurrence, with 80% globe salvage in those with recurrent solid tumor after IVC, 60% in those with recurrent subretinal seeds, and 88% in those with recurrent vitreous seeds.

The most striking benefit of IAC was observed when analysis was done by ICRB classification. There was excellent tumor control for Groups B and C retinoblastoma, with 100% globe salvage at 5 years compared with 86% in Group D and 55% in Group E (Figure).[12] This supports current practice, as IAC is generally reserved for Groups B, C, and D unilateral retinoblastoma, and occasionally Group E eyes.

Furthermore, analysis by age demonstrated better outcomes in younger patients (≤ 12 months vs > 12 months), including greater globe salvage rates (77% vs 72%, $P < .001$) and better vitreous seed control (90% vs 87%, $P = .036$).

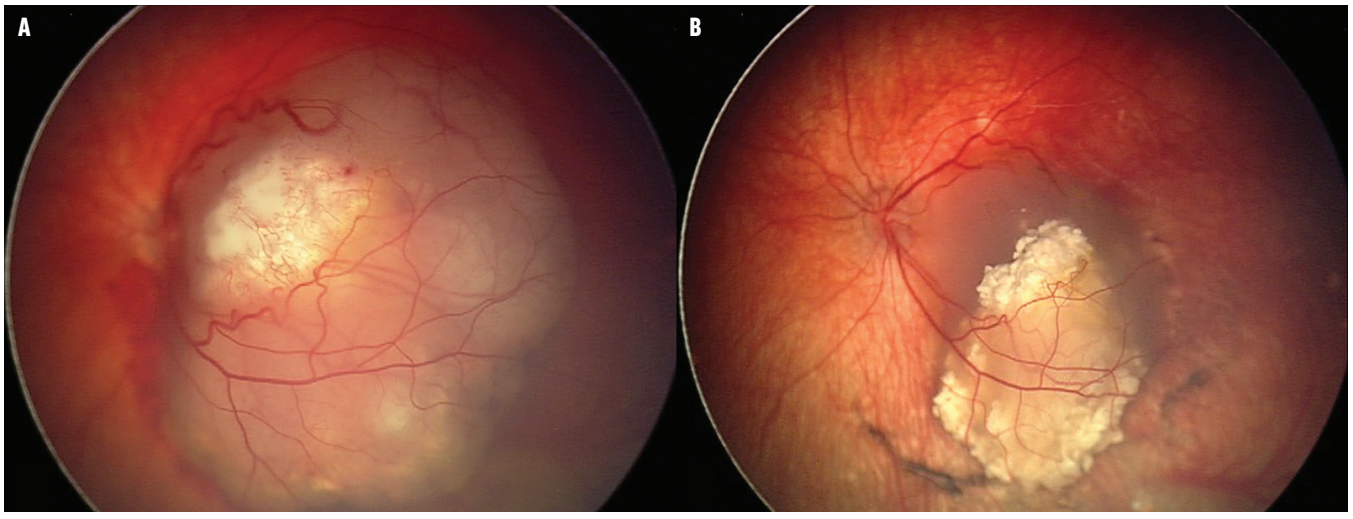


Figure. Fundus photography of an 11-month-old White infant shows a large, exophytic retinoblastoma (Group D) in the macular region of the left eye with feeder vessels, calcification, and subretinal hemorrhage (A). After receiving three infusions of IAC, the tumor completely regressed to a calcified scar with resolution of the subretinal hemorrhage (B).

Analysis by race and sex showed no statistically significant difference in treatment outcomes.

At our center, complications such as systemic side effects, ocular ischemia, neovascularization, and glaucoma were seen in approximately 1% or less of cases.

One limitation in our report was that, although all patients received IAC as their main treatment, some required additional therapies such as plaque radiotherapy, IVC, cryotherapy, and/or transpupillary thermotherapy for complete tumor control.

CONCLUSION

Chemotherapy, whether by intravenous, intraarterial, or intravitreous route, is a powerful treatment for retinoblastoma, as it provides reliable tumor control and globe salvage with few complications. At our center, we achieved globe salvage in 74% of all cases treated with IAC, with complications in approximately 1% or less. We hope that one day all patients with retinoblastoma will be evaluated at experienced centers that provide IAC as a treatment option so that more lives and eyes are saved, allowing children to surf through life cancer-free. ■

1. Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. *Indian J Ophthalmol*. 2020;68(11):2356-2365.
2. Abramson DH, Shields CL, Jabbour PJ, et al. Metastatic deaths in retinoblastoma patients treated with intraarterial chemotherapy (ophthalmic artery chemosurgery) worldwide. *Int J Retina Vitreous*. 2017;3:40.
3. Munier FL, Gaillard MC, Balmer A, et al. Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications. *Br J Ophthalmol*. 2012;96(8):1078-1083.
4. Manjandavida FP, Stathopoulos C, Zhang J, Honavar SG, Shields CL. Intra-arterial chemotherapy in retinoblastoma - A paradigm change [published correction appears in *Indian J Ophthalmol*. 2019;67(8):1385]. *Indian J Ophthalmol*. 2019;67(6):740-754.
5. Shields CL, Lally SE, Leahey AM, et al. Targeted retinoblastoma management. When to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. *Curr Opin Ophthalmol*. 2014;25(5):374-385.
6. Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology*. 2006;113(12):2276-2280.
7. Shields CL, Bas Z, Tadepalli S, et al. Long-term (20-year) real-world outcomes of intravenous chemotherapy (chemoreduction) for retinoblastoma in 964 eyes of 554 patients at a single centre. *Br J Ophthalmol*. 2020;104(11):1548-1555.
8. Shields CL, Manjandavida FP, Lally SE, et al. Intra-arterial chemotherapy for retinoblastoma in 70 eyes: outcomes based on the international classification of retinoblastoma. *Ophthalmology*. 2014;121(7):1453-1460.
9. Shields CL, Jorge R, Say EA, et al. Unilateral retinoblastoma managed with intravenous chemotherapy versus intra-arterial chemotherapy. Outcomes based on the International Classification of Retinoblastoma. *Asia Pac J Ophthalmol (Phila)*. 2016;5(2):97-103.
10. Munier FL, Mosimann P, Puccinelli F, et al. First-line intra-arterial versus intravenous chemotherapy in unilateral sporadic group D retinoblastoma: evidence of better visual outcomes, ocular survival and shorter time to success with intra-arterial delivery from retrospective review of 20 years of treatment. *Br J Ophthalmol*. 2017;101(8):1086-1093.
11. Dalvin LA, Ancona-Lezama D, Lucio-Alvarez JA, et al. Ophthalmic vascular events after primary unilateral intra-arterial chemotherapy for retinoblastoma in early and recent eras. *Ophthalmology*. 2018;125(11):1803-1811.
12. Shields CL, Dockery PW, Yaghy A, et al. Intra-arterial chemotherapy for retinoblastoma in 341 consecutive eyes (1292 infusions): Comparative analysis of outcomes based on patient age, race, and sex. *J AAPOS*. 2021 [In press].

FAIROOZ P. MANJANDAVIDA, MD
- Ophthalmic Oncologist, Ocular Oncology and Oculoplasty Services (FPM), Horus Specialty Eye Care, Bangalore, India
- Financial disclosure: None

ZAYNAB SAJJADI, BA
- Research Intern, Ocular Oncology Service, Wills Eye Hospital, Philadelphia
- zlsajjadi@gmail.com
- Financial disclosure: None

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

ANTONIO YAGHY, MD
- Research Intern, Ocular Oncology Service, Wills Eye Hospital, Philadelphia
- antonioyaghy@gmail.com
- Financial disclosure: None

Support provided in part by the Eye Tumor Research Foundation, Philadelphia, PA (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.

CYTOMEGALOVIRUS RETINITIS WITHOUT IMMUNOCOMPROMISE



What could have predisposed this immunocompetent patient to this complication with extensive retinal ischemia?

BY MICHAEL C. IZZO, MD; MARIAM MATHAI, MD; AND BRIAN K. DO, MD

Cytomegalovirus (CMV) retinitis, caused by a double-stranded DNA virus in the herpesviridae family, is the most common opportunistic ocular infection in patients with advanced AIDS.[1] CMV retinitis can occur in the absence of HIV infection, although this is uncommon. The retinitis in these cases is typically associated with relative immunosuppression with systemic corticosteroids, noncorticosteroid immunosuppressive agents, or chemotherapeutics.[2] CMV retinitis, in the absence of any systemic or local ocular immunosuppression, is extremely rare.[3-5]

Here, we present a case of CMV retinitis in a fully immunocompetent patient with significant widespread retinal ischemia in the affected eye.

CASE PRESENTATION

A 71-year-old Black man with a medical history including coronary artery disease, prostate cancer (treated by prostatectomy without chemotherapy or radiation), and quiescent sarcoidosis (off all treatment for 40 years) presented to a retina specialist for evaluation of decreased vision in the right eye for 3 weeks. The patient's ocular history was significant for cataract surgery with multifocal IOL implantation in both eyes and open-angle glaucoma treated with dorzolamide-timolol (2%/0.5%) and latanoprost (0.005%). He did not have a history of ocular sarcoid.

BCVA at presentation was counting fingers at 2 feet OD and 20/25 OS. IOP was 16 mm Hg in each eye, and a mild afferent pupillary defect was noted in the right eye.

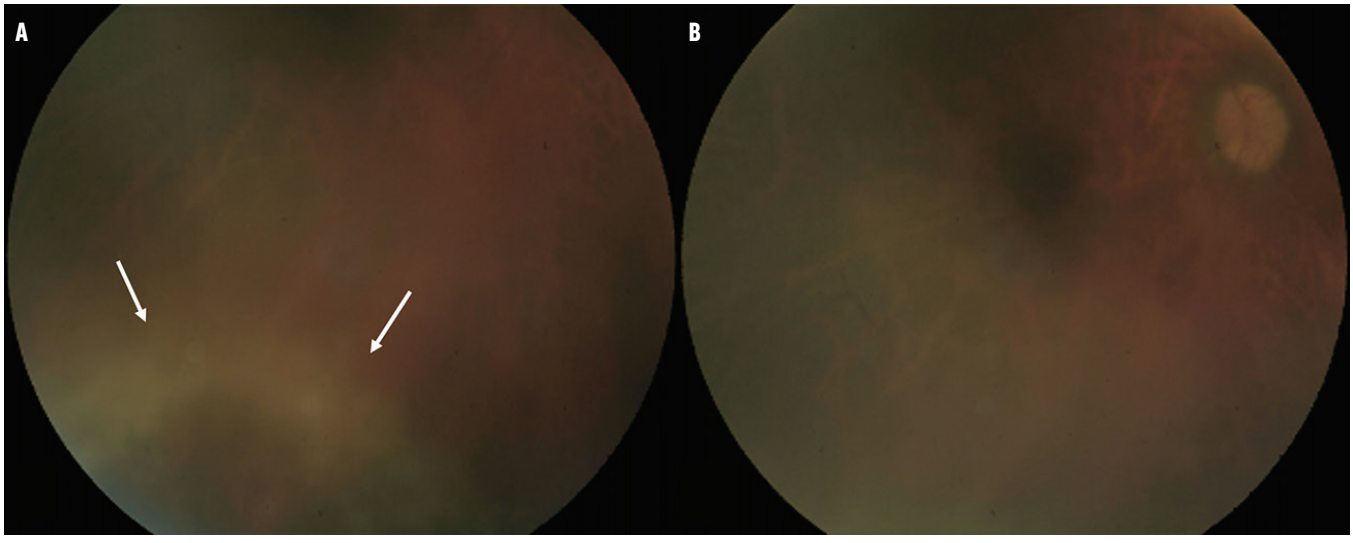


Figure 1. Color fundus photography of the right eye demonstrates peripheral yellow-white lesions (arrows) and retinal hemorrhage (A). A mildly pale, full optic nerve and significant arteriolar attenuation are also noted (B). Vitritis degrades the quality of the images.

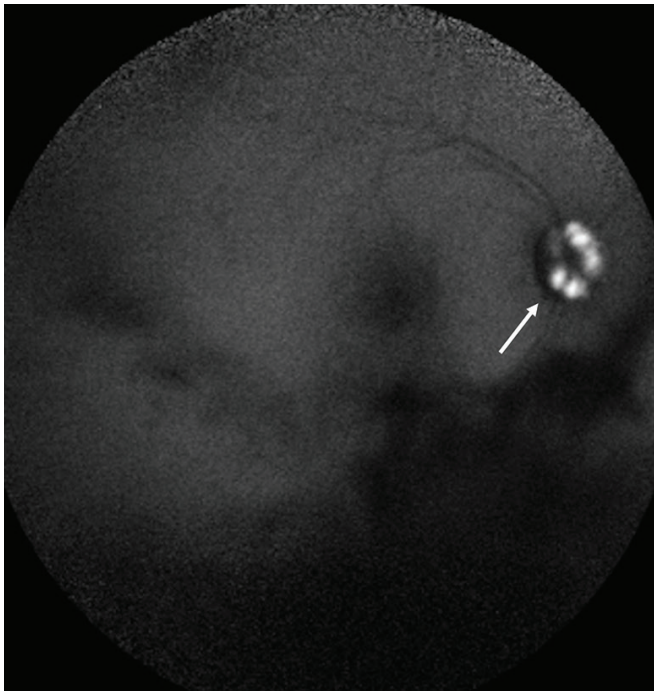


Figure 2. Fundus autofluorescence demonstrates hyperfluorescence of the optic nerve head consistent with optic nerve drusen (arrow).

Anterior segment examination of the right eye demonstrated keratic precipitates as well as 1+ cell and 1+ flare in the anterior chamber by Standardization of Uveitis Nomenclature criteria.[6] Fundoscopic examination of the right eye was limited due to significant vitreous haze; however, peripheral retinal whitening without any visible intraretinal hemorrhage was present and visible in the inferotemporal quadrant (Figure 1A). A mildly pale, full optic nerve and significant arteriolar attenuation were also noted (Figure 1B).

Slit-lamp and fundus examination of the left eye showed fullness of the optic nerve head. Fundus autofluorescence showed multifocal hyperautofluorescence of the optic nerve head in each eye, consistent with optic disc drusen (Figure 2). OCT of the macula showed band-like hyperreflectivity in the inner retinal layer and thickening consistent with acute ischemia, similar to findings described in paracentral acute middle maculopathy (Figure 3).[7] Fluorescein angiography showed extensive retinal nonperfusion (Figure 4).

DIFFERENTIAL DIAGNOSIS AND TREATMENT

The patient underwent diagnostic anterior chamber paracentesis and subsequent intravitreal injection of ganciclovir (4 mg/0.1 mL). Treatment with oral valacyclovir 2 g three times daily and trimethoprim 800 mg/sulfamethoxazole 160 mg twice daily was then initiated.

Aqueous fluid was analyzed via polymerase chain reaction (PCR) for herpes simplex virus 1 and 2, varicella zoster virus,

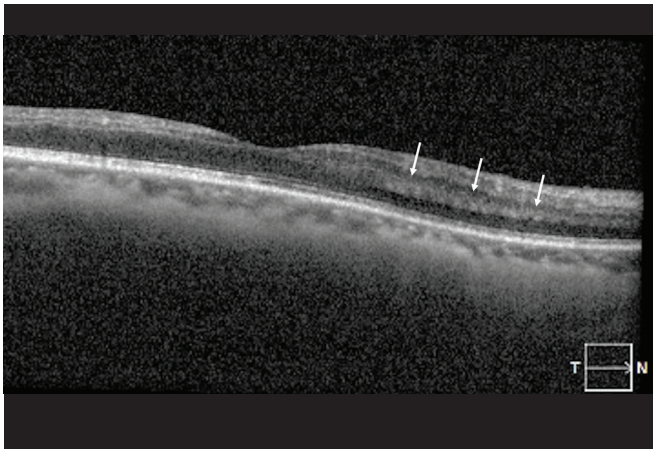


Figure 3. OCT of the right eye demonstrates band-like hyperreflectivity in the inner retinal layer (arrows) consistent with ischemia.

CMV, and *Toxoplasma gondii*. Serologic testing, including complete blood count with differential, comprehensive metabolic panel, Lyme antibodies, Quantiferon-TB Gold interferon-gamma release assay (Qiagen), rapid plasma reagin, and fluorescent treponemal antibody absorption were unrevealing. Chest radiograph was normal. Qualitative PCR analysis of the aqueous humor for CMV returned positive.

The patient subsequently received four weekly intravitreal injections of ganciclovir and a course of oral valganciclovir 900 mg twice daily for 2 weeks, at which time the dose of oral valganciclovir was reduced to 450 mg twice daily. The patient was also treated with topical prednisolone acetate 1% eye drops four times daily for 2 months, during which time the previously noted anterior chamber inflammation and vitritis improved significantly.

The extensive retinal nonperfusion noted upon initial evaluation persisted. The patient's vision remains stable at hand motion, with resolution of intraocular inflammation and the associated retinitis.

DISCUSSION

Ocular manifestations of CMV infection in immunocompromised patients have been extensively described. CMV reaches the retina hematogenously and infects the vascular endothelium, subsequently spreading to surrounding retinal cells.[1] The ocular examination classically reveals yellow-white retinal lesions beginning in the periphery that follow the vasculature centripetally. Retinal hemorrhage with surrounding whitish granularity is typical. Most patients do not present with vitritis, as they are severely immunosuppressed.

CMV retinitis has been reported in nonimmunosuppressed individuals after administration of local intraocular or periocular corticosteroid injections for other ocular disease; however, ocular CMV infection among patients without immune suppression is extremely rare.[3-5]

Although our patient had a history of sarcoidosis, he had not received any systemic or local immunosuppressive treatment at the time of his presentation to us or in the several months before presentation.

The extent of retinal ischemia seen in this patient is not typical for CMV retinitis, especially in the absence of widespread retinitis. There have been reports of acute retinal necrosis secondary to CMV with a mixed clinical picture of intraocular inflammation with panretinal occlusive vasculopathy, mostly in immunocompromised patients. One series included five non–HIV-positive patients presenting with granular necrotizing retinitis, vitritis, and severe occlusive vasculopathy.[5,8-10]

Our patient is likely on the clinical spectrum of those previously reported cases. The presence of optic nerve head drusen may also have predisposed our patient to the development of widespread retinal nonperfusion, as this type of disc change has been associated with decreased perfusion of the optic nerve head.[10]

CONCLUSION

This case demonstrates the importance of immediate empiric treatment for CMV and continued testing for CMV in aqueous PCR in all patients presenting with retinitis, even those who are immunocompetent. ■

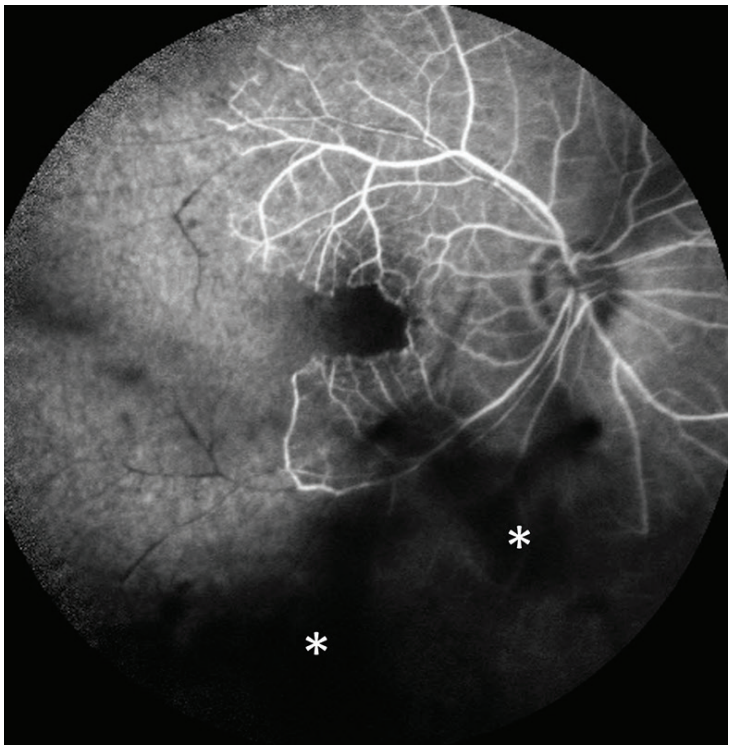


Figure 4. Fluorescein angiography of the right eye demonstrates extensive late-phase peripheral and macular capillary nonperfusion, as well as blocking from vitreous debris (stars).

1. Port A, Orlin A, Kiss S, Patel S, D'Amico DJ, Gupta MP. Cytomegalovirus retinitis: a review. *J Ocul Pharmacol Ther*. 2017;33(4):224-234.
2. Gupta S, Vemulakonda G, Suhler E, et al. Cytomegalovirus retinitis in the absence of AIDS. *Can J Ophthalmol*. 2013;48(2):126-129.
3. Karkhaneh R, Lashay A, Ahmadraji A. Cytomegalovirus retinitis in an immunocompetent patient: A case report. *J Curr Ophthalmol*. 2016;28(2):93-95.
4. Radwan A, Metzinger J, Hinkle D, Foster C. Cytomegalovirus retinitis in immunocompetent patients: case reports and literature review. *Ocul Immunol Inflamm*. 2013;21(4):324-328.
5. Schneider EW, Elner SG, van Kuijk FJ, et al. Chronic retinal necrosis: cytomegalovirus necrotizing retinitis associated with panretinal vasculopathy in non-HIV patients. *Retina*. 2013;33(9):1791-1799.
6. Trusko B, Thorne J, Jabs D, et al. The Standardization of Uveitis Nomenclature (SUN) Project. Development of a clinical evidence base utilizing informatics tools and techniques. *Methods Inf Med*. 2013;52(3):259-265.
7. Chen X, Rahimy E, Sergott RC, et al. Spectrum of retinal vascular diseases associated with paracentral acute middle maculopathy. *Am J Ophthalmol*. 2015;160(1):26-34.e1.
8. Pathanapitoon K, Tesavibul N, Choopong P, et al. Clinical manifestations of cytomegalovirus-associated posterior uveitis and panuveitis in patients without human immunodeficiency virus infection. *JAMA Ophthalmol*. 2013;131(5):638-645.
9. Saran BR, Pomilla PV. Retinal vascular nonperfusion and retinal neovascularization as a consequence of cytomegalovirus retinitis and cryptococcal choroiditis. *Retina*. 1996;16(6):510-512.
10. Obuchowska I, Ustymowicz A. Blood flow disturbances in the central retinal artery in patients with bilateral optic disc drusen. *Sci Rep*. 2020;10:1111.

BRIAN K. DO, MD
- Retina and Uveitis Specialist, The Retina Group of Washington, Fairfax, Virginia
- Assistant Professor of Ophthalmology, Georgetown University School of Medicine, Washington
- bdo@rgw.com
- Financial disclosure: None

JORDANA G. FEIN, MD, MS, SECTION EDITOR
- Retina Specialist, The Retina Group of Washington, Fairfax, Virginia
- Assistant Professor of Ophthalmology, Georgetown University School of Medicine, Washington
- Co-Founder, International Society for the Advancement of Medical Retina
- jfein@rgw.com
- Financial disclosure: Consultant (Regeneron, Bausch + Lomb)

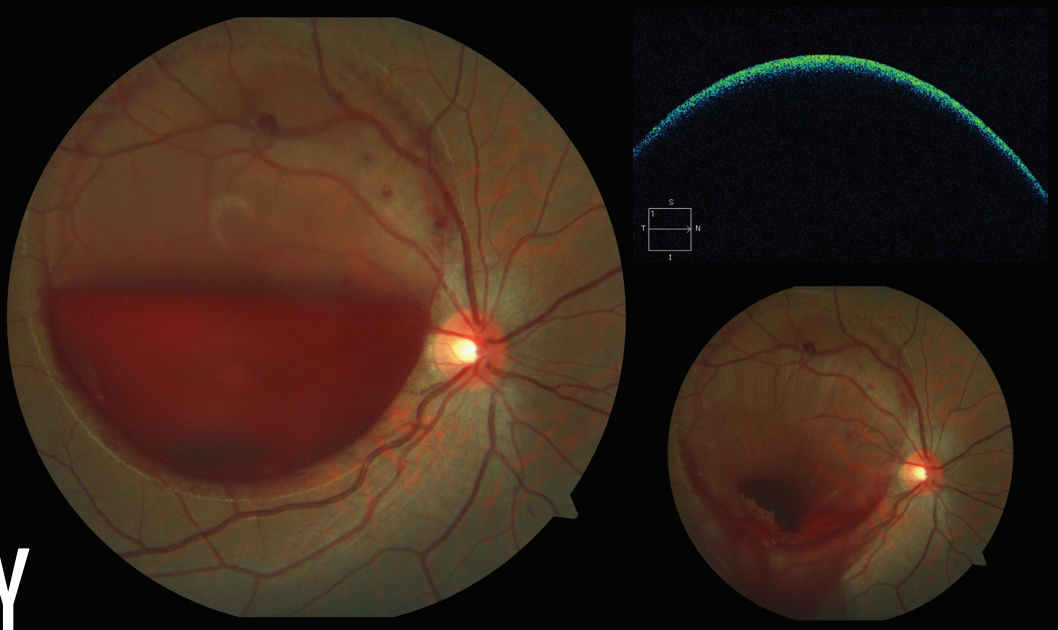
MICHAEL C. IZZO, MD
- Ophthalmology Resident, MedStar Georgetown University Hospital and Washington Hospital Center, Department of Ophthalmology, Washington
- mikec.izzo@gmail.com
- Financial disclosure: None

MARIAM MATHAI, MD
- Retina Fellow, The Retina Group of Washington and Washington Hospital Center, Department of Ophthalmology, Washington
- mathaim90@gmail.com
- 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)

Authors' note: Consent to publish this case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

TRACKING A CASE OF VALSALVA RETINOPATHY



A new predictive tool could help clinicians catch complications after laser membranotomy.

BY KUSHAL DELHIWALA, MBBS, MS, FMRF, FICO

A 26-year-old man presented with sudden, painless loss of central vision in the right eye for 1 day following an episode of vomiting. BCVA was 20/200 OD. Fundus evaluation revealed a massive boat-shaped premacular hemorrhage in the right eye associated with a glistening reflex, suggestive of blood in the sub-internal limiting membrane (ILM) space (Main Figure).

The spectral-domain OCT (SD-OCT) raster scan showed the convex premacular hemorrhage with shadowing beneath (Inset, Top). The patient was diagnosed with Valsalva retinopathy and underwent same-day laser membranotomy.

FOLLOW-UP

Following membranotomy, blood was noted trickling inferiorly into the vitreous (Inset, Bottom). BCVA improved to 20/30 OD at 10 days after membranotomy and 20/20 OD at 40 days. There was gradual complete drainage of the premacular hemorrhage along with ILM striations but no metamorphopsia. The associated inferior vitreous hemorrhage resolved by 6 weeks.

SD-OCT at 10 and 40 days after membranotomy showed a healthy foveal dip and a persistent hyporeflective premacular sub-ILM cavity measuring 588 µm and 820 µm, respectively (Figure, next page, Top and Top Middle). The ILM architecture and the height of the premacular sub-ILM cavity were measured by a vertical line perpendicular to the tangential lines passing through the foveola and the highest point of the sub-ILM cavity.

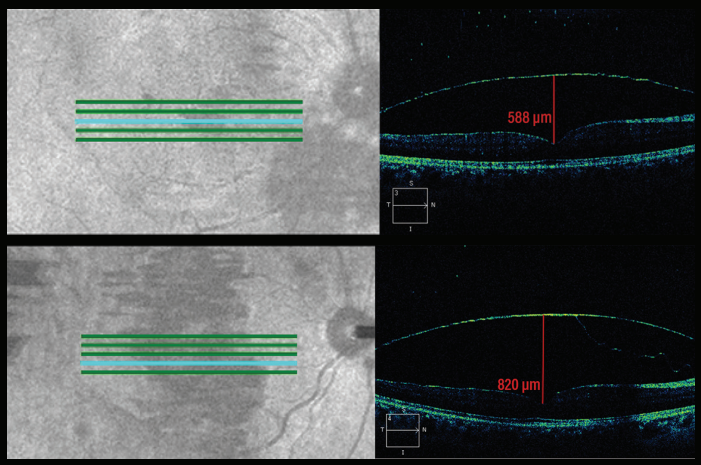
SD-OCT also revealed an unsealed laser perforation site in the inferotemporal perifoveal region and the absence of a posterior vitreous detachment (PVD).

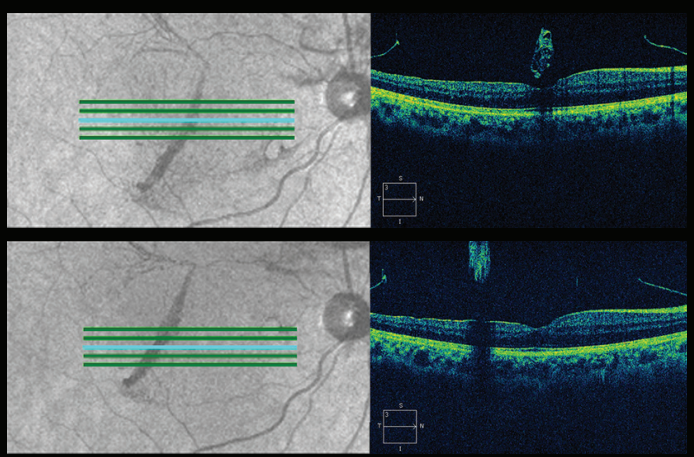
At 4 months, SD-OCT revealed wrinkling and falling back of the ILM toward the surface of the neurosensory retina, corresponding with posterior hyaloid detachment from the ILM marked by two separate hyperreflective layers. The sub-ILM cavity height increased significantly to 820 µm.

At 10 months, the sub-ILM cavity collapsed with a curled-up, mobile ILM remnant hanging above the fovea due to focal retinal attachment, suggestive of complete macular PVD (Figure, next page, Bottom Middle). At 24 months, BCVA was stable at 20/20 OD without metamorphopsia. SD-OCT showed persistence of the ILM remnant with focal retinal attachment (Figure, next page, Bottom).

DISCUSSION

Valsalva retinopathy is commonly characterized by subhyaloid/sub-ILM hemorrhage.[1,2] It occurs following a sudden rise in intrathoracic pressure (Valsalva maneuver) that transmits to the superficial retinal vessels, leading to their rupture. A persistent premacular sub-ILM cavity following laser membranotomy in Valsalva retinopathy has been reported with varied hypotheses.[3,4] Firm adhesion of the posterior hyaloid to the ILM in young patients can cause a sub-ILM cavity in the acute stage. Increased height of this cavity over 6 to 8 months, measured on OCT, can be a predictor of evolving PVD and subsequent resolution of the cavity. ■





1. Duane TD. Valsalva hemorrhagic retinopathy. *Trans Am Ophthalmol Soc*. 1972;70:298-313.
2. Shukla D, Naresh KB, Kim R. Optical coherence tomography findings in Valsalva retinopathy. *Am J Ophthalmol*. 2005;140:134-136.
3. Zou M, Gao S, Zhang J, Zhang M. Persistent unsealed internal limiting membrane after Nd:YAG laser treatment for Valsalva retinopathy. *BMC Ophthalmol*. 2013;13:15.
4. Sabella P, Bottoni F, Staurenghi G. Spectral-domain OCT evaluation of Nd:YAG laser treatment for Valsalva retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(4):599-601.

KUSHAL DELHIWALA, MBBS, MS, FMRF, FICO
- Vitreoretina Consultant, Netralaya Super Speciality Eye Hospital, Ahmedabad, India
- kushal.delhiwala@yahoo.co.in
- Financial disclosure: None

MANISH NAGPAL, MBBS, MS, FRCS, SECTION EDTIOR
- 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

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.

NETAN CHOUDHRY, MD, FRCSC

Can you tell us about the first time you realized you wanted to become an ophthalmologist?

As a medical student at Georgetown University, I had the opportunity to rotate through the ophthalmology department. This was one of my first exposures to the field, and I was taken by the integration of technology and surgery as well as the diversity of patient types. This definitely supercharged my interest in a career in ophthalmology. I subsequently had the privilege of spending a month rotating with Larry Singerman, MD, FACS, in Cleveland where I was exposed to a dynamic retina practice. The rest, as they say, is history.

What led you to specialize in retinal imaging and rare disorders of the retina and vitreous?

As a resident at the University of Pennsylvania Scheie Eye Institute, I was fortunate to learn under many brilliant minds, most notably, Alexander J. Brucker, MD. He and I embarked on a project together looking at the discrepancy between leakage on fluorescein angiography and OCT. Through this exercise, I had a chance to really dive into the complex arena of retinal imaging, to work closely with the photographers, and to appreciate the technical aspects of image capture and evaluation. I completed my fellowship in vitreoretinal surgery at the Massachusetts Eye and Ear of Harvard Medical School, where my enthusiasm expanded. Working alongside international fellows and faculty, I explored the strengths and limitations of various devices and realized how subtle aspects of retinal images could provide valuable insights into disease and patient prognosis. To me, looking at these retinal images was like looking into space and seeing the cosmos.

You pioneered OCT imaging of the peripheral retina, and you have developed novel noninvasive devices for imaging the retina and vitreous. What have you learned from these experiences?

The journey of research and innovation is a team effort, and I have worked alongside several bright individuals who helped steer the ship. Exploring the peripheral retina, the examination of which for many is not only difficult but intimidating, has been an enjoyable challenge. I am fortunate to have connected my enthusiasm for imaging the peripheral retina with innovation, and I have worked alongside device companies to create novel equipment. The arduous journey of taking an idea to completion has shown me the value of patience, flexibility, and, most important, perseverance.

Where do you see new developments in ocular imaging technology occurring in the coming years?

Ocular imaging has come a long way since the introduction of the traditional fundus camera and OCT imaging, from ultrawide-field imaging and autofluorescence to OCT angiography. The future of imaging is bright! We are beginning to see improvement in adaptive optics technology to enable us to visualize individual cells in the retina and, of course, the integration of machine learning or AI into our commonly used devices. The goal of our field has always been to advance the frontier of medicine by working alongside our technology to eradicate blindness, and I see the possibility of this in the near future.

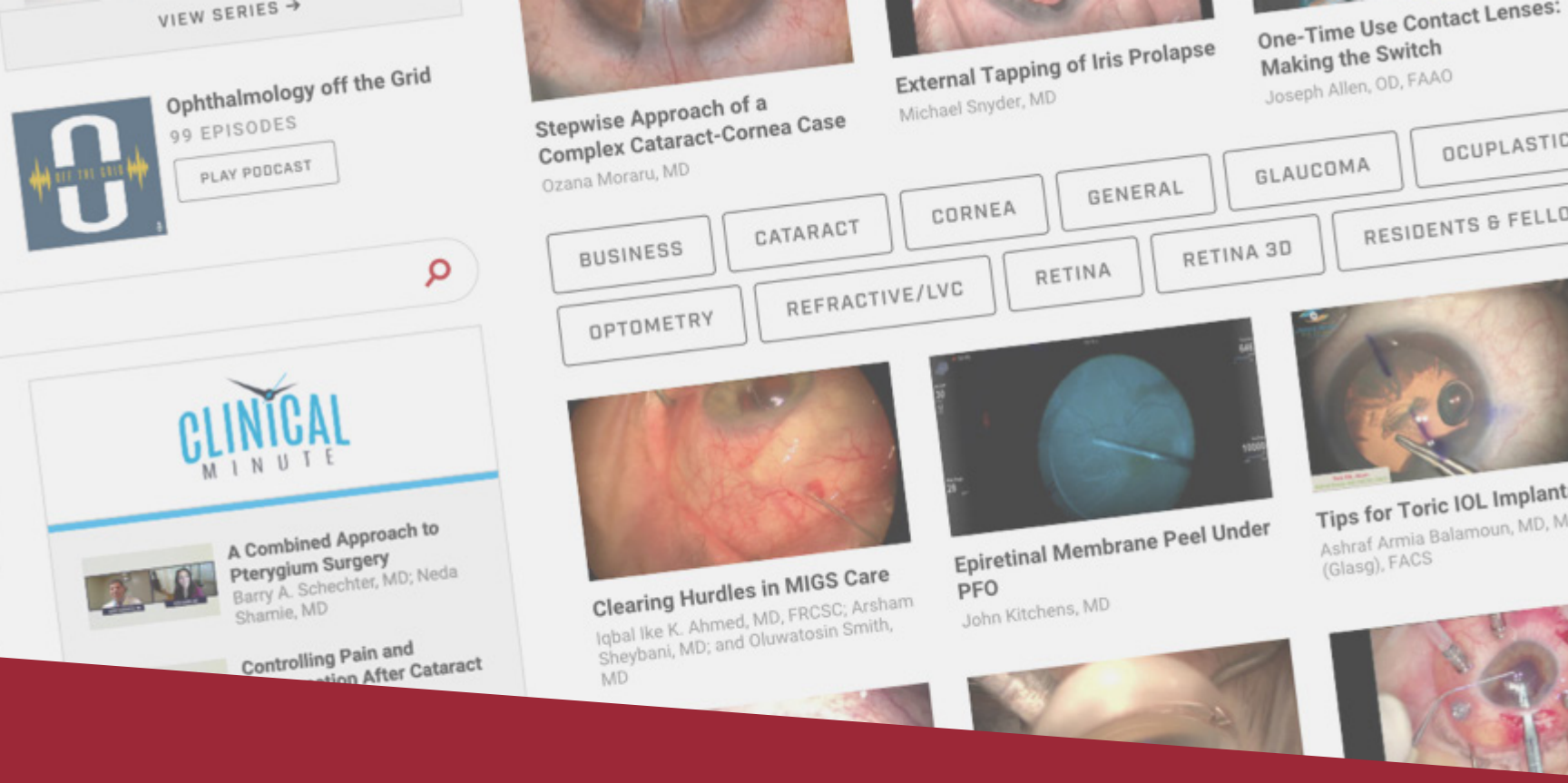
Figure. Dr. Choudhry and his family enjoying a day in the park.

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

In all honesty, there is no single most memorable experience. I have had great mentors and colleagues, each of whom has shaped my professional career. Each patient in whom I am able to help restore sight is the most memorable experience of that day. The tapestry of intertwining patient stories motivates me to carry forward with my peers and strive to give sight to the blind. I find that these patient encounters are the most lasting memories. ■

NETAN CHOUDHRY, MD, FRCSC

- Co-Founder and Medical Director, Vitreous Retina Macula Specialists of Toronto
- netan.choudhry@gmail.com
- Financial disclosure: Advisor (Bayer, Novartis, Optos, Roche, Topcon); Research Support (Bayer); Research Equipment (Carl Zeiss Meditec, Topcon); Speaker (Allergan, Bayer, Optos, Topcon)



HAVE YOU SEEN THE NEW EYETUBE?

Eyetube has just been completely updated with new features and a streamlined look—all designed to keep you informed of the latest procedures, techniques, devices, and more in ophthalmology.

Visit Eyetube.net to explore to more than 8,000 videos.

eyetube | bmc

Genentech
A Member of the Roche Group

LOOK BEYOND THE LIMITS
IN OPHTHALMOLOGY

THE
WINDOW
TO CHANGE

M-US-00009911(v1.0) 2/21