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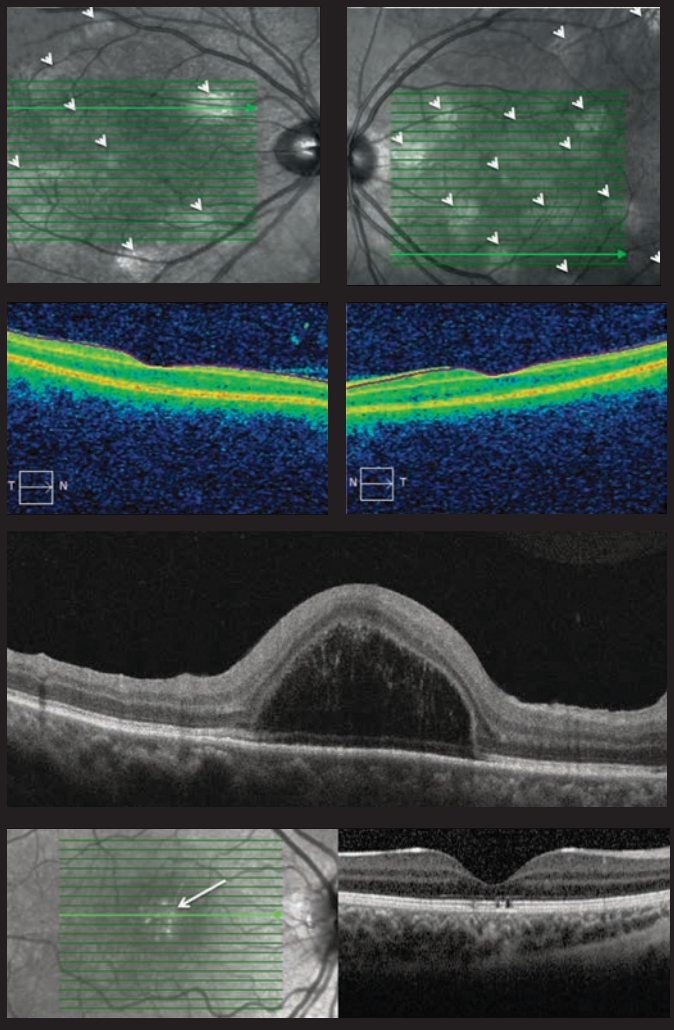
RETINA SPECIALIST

VOL. 6, NO.5 • SEPTEMBER/OCTOBER 2020

Imaging Forum: Symptoms betray common masquerader Page 9

Page 14 Uveitis Forum: Pars plana vitrectomy in the management of uveitis



SIGNATURE OCT FINDINGS AS A DIAGNOSTIC TOOL

How imaging helped to identify four novel pathologies – Page 18

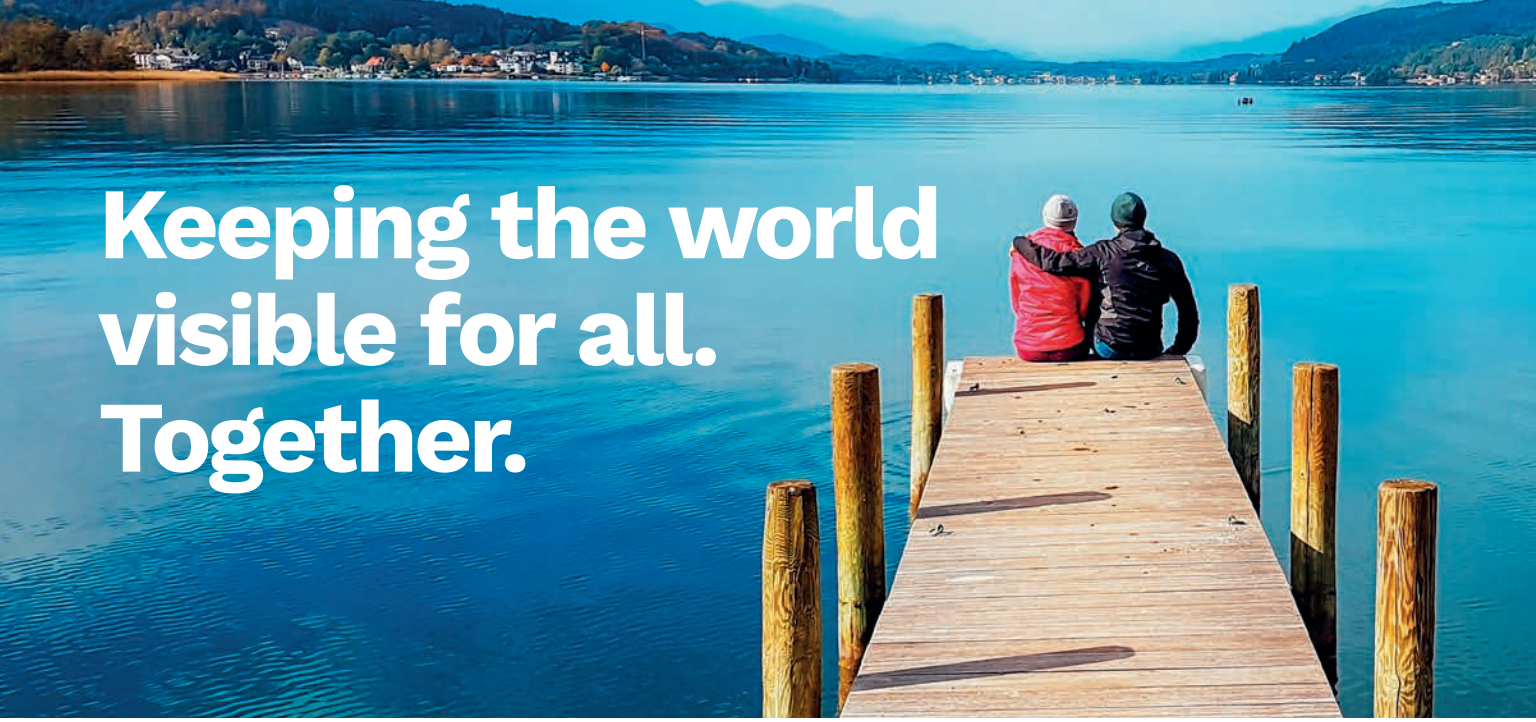
Also Inside

Understanding the role of Ang2 in nAMD – Page 24

How UWF imaging can guide anti-VEGF therapy in PDR – Page 28

Report from ASRS 2020 – Page 33

Online Video **Pearls for intraocular foreign body removal** – Page 16



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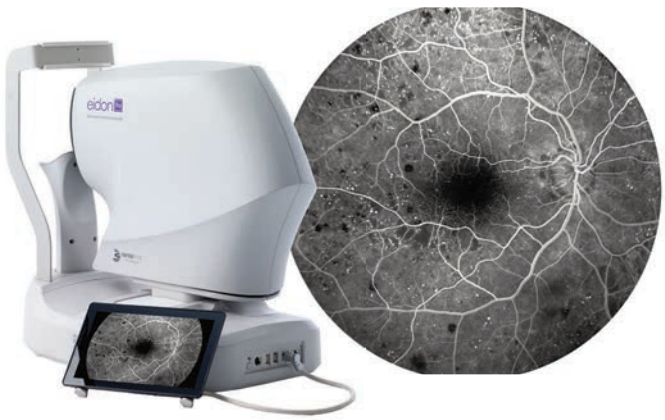

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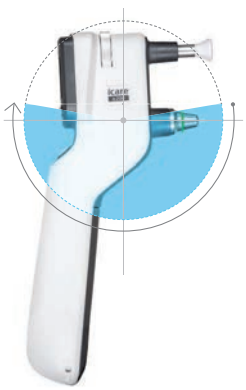

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EDITORIAL

By Charles C. Wykoff, MD, PhD

The anxiety around us

COVID-19 continues to rage. Fortunately, through the late summer weeks, many urban areas saw declines in the rates of new infections and deaths. Forward progress with vaccine development has also brought positive news.

Nevertheless, health-care systems continue to strain under the weight of disease management. Families continue to endure challenges induced by isolation, virtual learning and job insecurity.

This pandemic is having profound psychological consequences. Distress and fear of contagion, particularly among health-care professionals, are real whether we consciously recognize them or not. Social isolation, uncertainty and the possibility of economic loss compound the situation and can lead to the development or exacerbation of depression, insomnia, anxiety, substance abuse and suicide.

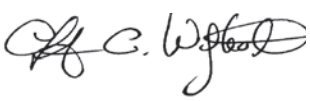
The Spanish Flu of 1918-19, in which about one-third of the world's population were infected and at least 50 million perished, was associated with an increase in suicide, as was the 2003 severe acute respiratory syndrome outbreak, particularly among those 65 and over. Some have sounded the alarm for an anticipated increase in suicides due to COVID-19.

As physicians we are natural leaders in this crisis and have the skills to be the support our society so badly needs. Have a heightened sense of awareness of instability among your families, colleagues, staff and patients. Please go out of your way to make sure those in your circle are not alone in their isolation and stress. Recognize that the anxiety and fear we are walking through is real and encourage those around you to do the same.

Even if you're psychologically well—possibly better than ever because your job is secure, your investments are doing well and you're spending more time with family because meetings have transitioned to a virtual format—realize that many others you directly come into contact with at work or the grocery store are living in a very different, colder and harsher reality.

I charge you to reach out. Don't wait for someone else to call. Be the one to call a friend or sibling you haven't connected with in too long. Small gestures go a long way to stabilize emotions in a tumultuous time.

None of us have lived through a situation like this. We're all learning as we go and the road is fraught with challenges. But if we allow ourselves to honestly recognize the powerful psychological stressors that rage around us, we can address them and proactively strengthen our extended support networks—ultimately the foundation for a well-adjusted, prosperous society. RS



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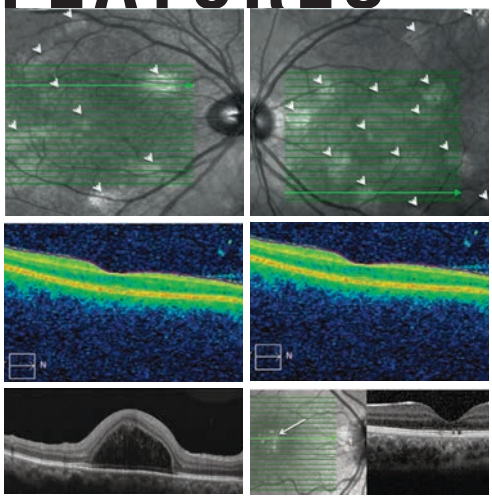
SEPTEMBER/OCTOBER 2020 • VOL. 6, NO. 5

FEATURES



18
COVER STORY:
Signature OCT findings as a diagnostic tool
How imaging helped diagnose four novel retinal pathologies.
By Juliet Essilfie, MD, and Yasha Modi, MD

24
Understanding role of Ang 2 in neovascular AMD
Angiopoietin-2 is an increasingly desirable target in age-related macular degeneration. Here's why.
By Eric Williams, MD, Matthew Powers, MD, MBA, and Jeffrey Olson, MD

28
How UWF imaging can guide anti-VEGF therapy in PDR
A report on our experience using ultra-widefield imaging to evaluate endolaser-less vitrectomy for vitreous hemorrhage.
By Venkatkrish M. Kasetty, MD, Davis Starnes and Dennis M. Marcus, MD

33
Retina Standouts from ASRS 2020: Novel approaches to PVR, RP and macular hole surgery
Five noteworthy presentations from the virtual gathering of global retina specialists.
By Ashkan M. Abbey, MD

DEPARTMENTS

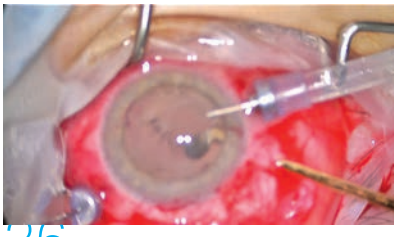
3 **Editor's Page**
The anxiety around us
By Charles C. Wykoff, MD, PhD

7 **Retina Update**
Why we need more precise terminology for race, ethnicity

9 **Imaging Forum**
Symptoms betray a common masquerader
Edited by Jason Hsu, MD

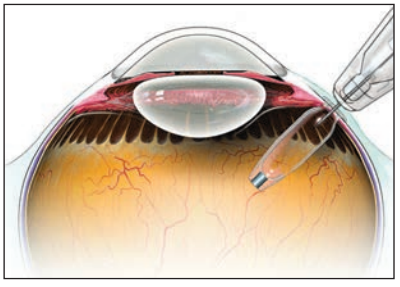
14 **Uveitis Forum**
PPV in the management of uveitis
Edited by Akshay S. Thomas, MD, MS

16 **Surgical Pearl Video**
Online Video
Pearls for foreign body removal
Edited by Paul Hahn, MD, PhD



36 **Coding Commentary**
ng the web of 'bundles'
By Ellen R. Adams, MBA

37 **Clinical Trial Closeup**
h ranibizumab:
It's in the technique
Edited by Emmett T. Cunningham Jr., MD, PhD



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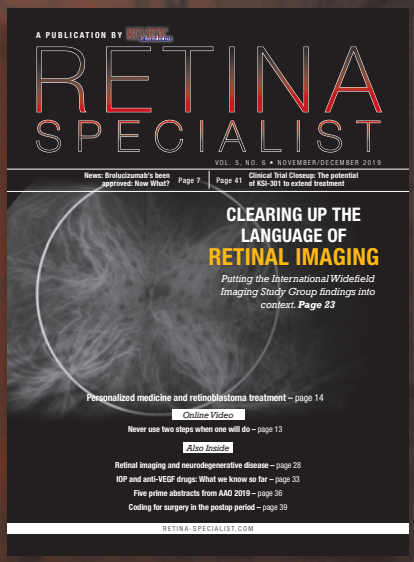

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Why we need more precise terminology for race, ethnicity

Daniel B. Moore, MD, an associate professor of ophthalmology at the University of Kentucky in Lexington, admits that he's somewhat uncomfortable being in the position of talking about race and ethnicity in the ophthalmology literature, and even that he has a "very limited understanding" of it. But he's also the only one talking about it.

Last month he published a cross-sectional study in *JAMA Ophthalmology* of how race and ethnicity were reported in the ophthalmology literature last year.[1] He found a number of inconsistencies in how researchers define and reference the race and ethnicity of study subjects. A total of 78 races or ethnicities were defined in the few studies that included race and ethnicity.

A social construct

"Clearly, I'm not an expert in this, and I shouldn't be an authority figure," Dr. Moore tells *Retina Specialist*. "I think, hopefully, it is quite clear and apparent to anyone who looks into it that the notion of race is not biologic; it's a social/political construct." That construct "served political, and social and economic purposes," he says. "Science got involved and helped to propagate some of the racial theories that are still with us today."

Daniel B. Moore, MD, questions how the literature references race and ethnicity.

The idea for the study came to him when he read Angela Sciani's *Superior, The Return of Race Science* (Penguin Random House), which explores how science embraced race to describe biological differences between peoples.

"She's arguing that if we're going to use race as a proxy in our scientific literature, we need to at least know what we're talking about," he says. "We at least need to be consistent so that people understand and discern what the topic is at hand. And she argues that that's not necessarily the case in most of science."

So Dr. Moore evaluated how articles published last year in the *American Journal of Ophthalmology*, *JAMA Ophthalmology and Ophthalmology* referenced race and ethnicity. Of 547 articles, only 42 percent (233) reported race and/or ethnicity. Only 4.4 percent (30 studies) actually described how they defined race/ethnicity.

'Nebulous terms'

"Race and ethnicity are very nebulous terms that are defined differently by different people, in different times and different places," he says. "To just throw them into an article without really trying to characterize or describe what you're measuring also has the potential to limit the applicability of your data."

"Some governing bodies," he notes, including the National Institutes of Health, have regulations on what race and ethnicity mean. "But even then," he adds, "when you look at papers in our literature that follow NIH guidelines or are supported by the NIH, they're not being utilized with much rigor."

As his study points out, some authors describe as *ethnicity* what the NIH defines as *race* and vice versa. "Or they clump into one group race/ethnicity, or they use heterogeneous terms such as *population* or *descent*. It makes it hard to address this issue in

IN BRIEF

The Food and Drug Administration has granted fast-track designation to **GT005**, **Gyroscope Therapeutics'** investigative treatment for geographic atrophy secondary to dry age-related macular degeneration. GT005 is a one-time adeno-associated virus (AAV)-based gene therapy delivered under the retina. The Phase II EXPLORE trial is enrolling. A second Phase II trial in a broader group of GA patients is also planned.

NR082 (**Neurophth Therapeutics**) received FDA orphan drug designation for Leber hereditary optic neuropathy associated with ND4 mutation. NR082 uses an AAV2 vector to express human ND4 gene in retinal ganglion cells to repair optic neuropathy caused by 11778 G>A mutation.

Alimera Sciences has enrolled the first patient in the NEW DAY trial of **Iluvien** (fluocinolone acetonide intravitreal implant) 0.19 mg as a baseline therapy for diabetic macular edema. The trial plans to enroll around 300 treatment-naive or almost naive DME patients.

RegenxBio has dosed the first patient in the AAVIATE Phase II trial to evaluate suprachoroidal delivery of the AAV gene therapy **RGX-314** with the **SCS Microinjector** (**Clearside Biomedical**) for wet AMD.

any uniform manner."

The challenge for science is using race or ethnicity in the physiological context—whether they're interpreted as biologic, anatomic or genetic—as outcomes measures.

"The onus should be on us as a community and investigators to demonstrate why that is necessary, not vice versa," he says. "We should not take any of that for granted. We really have to be rigorous in accessing why it's being evaluated in the first place."

Why it matters

However, referencing race or ethnicity, or both, in the literature can help providers and policymakers to better understand health disparities among socioeconomic groups, the so-called social determinants of health—disparities made all the more obvious in the COVID-19 pandemic.

"Just by saying that race is not scientific does not mean that race is not real," Dr. Moore says. "Race is very, very real, and it has real effects on individuals and populations, and that's where the social determinants of health care come into play."

Science can't address those disparities if it ignores race and ethnicity, he says. "So, first, being able to acknowledge disparities exist, but then trying to delve into why they do and what needs to be done about them are within the lane of scientists and researchers and those in health care."

But, he emphasizes, the language used to reference race and ethnicity needs to be consistent. That may not be easy, but it's important.

"It's important because you want to ensure that the populations that are being evaluated are inclusive and representative, one, of the proposed population, but then, two, can be brought back to an individual practitioner's own patients," he says. For example, a large study in the northern Midwest would likely involve a largely white population, the findings of which may not be transferable to a practice in an urban center in the Northeast or South. "But being aware of that information and the potential limitations is very important so that you can take that under consideration," he says.

Role in research

Clear definitions of race and ethnicity would also aid researchers in recruiting more representative study populations. "If a research study has a demographic that doesn't seem appropriate for that particular area, you have to question why that may be—whether there's no access, whether certain groups or individuals are feeling marginalized and, for a variety of reasons, don't feel comfortable participating in research studies," Dr. Moore explains. "We want to ensure that all those who can have the opportunity to participate and then gain from the benefits of research."

Defining those parameters is a global task. "As our literature is becoming more and more global, as we're being more inclusive of communities outside of our own country, it makes this an all the more complicated picture," Dr. Moore adds. "We need to at least to try to have some measures of how we're going to address this, and it likely would involve a global audience. So, this shouldn't be a small group of academics from an institution here in America. It needs to be a very broad and inclusive group."

This White associate professor from middle America who admits he's a beneficiary of racial privilege may seem like an unlikely person to sound that clarion call, but so far he's the only one. RS

— Richard Mark Kirkner

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Symptoms betray common masquerader

OCT imaging has made it possible to report pathognomonic features that include punctate hyperreflectivity in the choroid.

By Samir N. Patel, MD; Jason Hsu, MD


Samir N. Patel, MD


Jason Hsu, MD

A 39-year-old man was referred to the retina clinic for evaluation of blurred vision in both eyes. He reported progressive floaters in the left eye over the past two weeks and was diagnosed with a posterior vitreous detachment in the left eye by an outside provider.

Since that diagnosis, he reported progressive floaters in the right eye. His medical and ocular history were unremarkable, but he was taking emtricitabine/tenofovir (Truvada, Gilead) for pre-exposure prophylaxis of HIV.

Work-up and imaging findings

At the initial visit to the retina clinic, the patient's visual acuity was 20/60 OD and 20/70 OS. Intraocular pressures were normal. The anterior segment was notable for 2+ cell bilaterally. The anterior vitreous was notable for 1+ cell OD and trace cell OS.

Fundus examination revealed bilateral large placoid macular lesions (*Figure 1*). Fundus autofluorescence disclosed bilateral hyperautofluorescence of the placoid macular lesions and areas of speckled hyperautofluorescence nasally (*Figure 2, page 10*).

Fluorescein angiogram revealed bilateral hyperfluorescent staining of the placoid macular lesions and irregular hyperfluorescence nasally as well as some focal staining of the vessels and hyperfluorescence of the optic nerves (*Figure 3, page 10*). Optical coherence tomography revealed bilateral diffuse outer segment irregularity with widespread disruption of the outer retinal layers and hyperreflective nodular retinal pigment epithelium lesions (*Figure 4, page 11*).

Additional history and diagnosis

The patient's social history was notable for multiple sexual partners. Four months prior to presentation, he had a routine screening with negative HIV and syphilis enzyme immunoassay testing. Despite the recent negative syphilis testing, the patient's clinical examination was highly suspicious for bilateral acute syphilitic placoid posterior chorioretinopathy.

Hospital admission and labs

He was admitted to the hospital for suspicion of ocular syphilis. A repeat syphilis immunoassay test on admission was positive with a reflex reactive rapid plasma reagin (RPR) titer of 1:256. Repeat HIV and testing of other sexually transmitted diseases was negative.

Infectious disease was consulted and recommended a lumbar puncture and initiation of intravenous penicillin (24 million units per day) for 14 days. He was

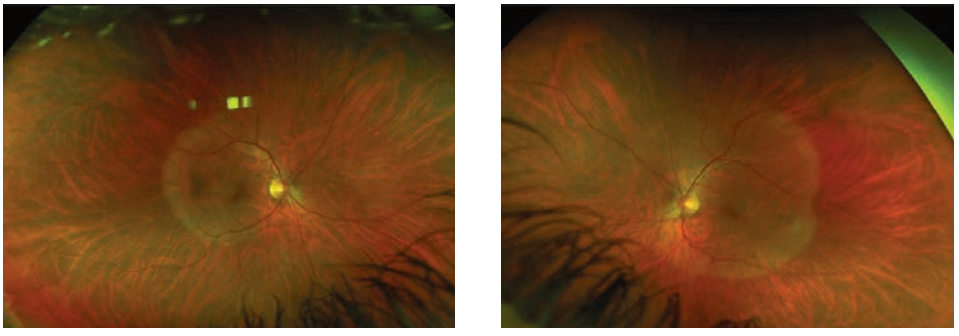

Figure 1. Fundus examination revealed bilateral large placoid macular lesions.

Bios

Dr. Hsu is with Mid Atlantic Retina/Retina Service, Wills Eye Hospital, Philadelphia, where Dr. Patel is a first-year vitreoretinal fellow.

DISCLOSURES: Drs. Hsu and Patel have no relevant financial relationships to disclose.

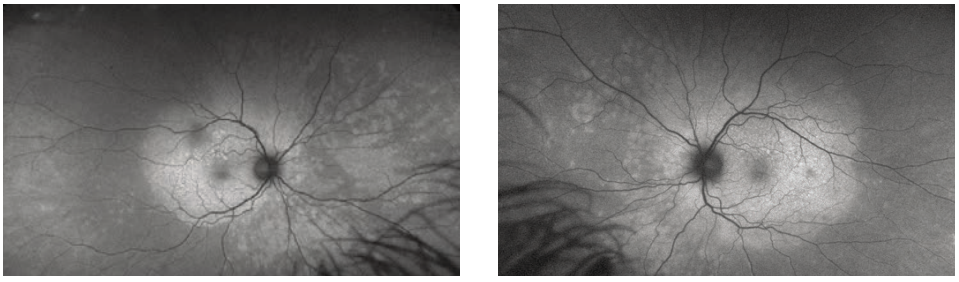

Figure 2. Fundus autofluorescence disclosed bilateral hyperautofluorescence of the placoid macular lesions and areas of speckled hyperautofluorescence nasally.

also started on topical prednisolone acetate six times per day in both eyes for the anterior chamber inflammation.

Follow-up

Three weeks after the initial visit, the patient's visual acuity improved to 20/25 OD and 20/40 OS. Intraocular pressures were normal. The anterior segment was quiet bilaterally.

Fundus examination revealed resolution of the bilateral large placoid macular lesions. OCT revealed reconstitution of the outer retinal segments and disappearance of the hyperreflective nodular RPE lesions (*Figure 5, page 12*). He was tapered off the topical steroids over one month, and he was concurrently followed by an infectious disease specialist, who noted progressive decline of the RPR titer at three months post-treatment.

A modern epidemic

Although syphilis was first recognized in Europe in the late 15th century, there has been a significant increase in the number of cases worldwide, including in the United States. The Centers for Disease Control and Prevention reporting an 81-percent increase from 2014 to 2018.[1-3]

Known as "the great masquerader," ocular syphilis can occur in nearly any ocular structure as early as six weeks after transmission and may often be the only sign of systemic syphilis.[4]

Most patients with ocular syphilis have posterior uveitis as the primary manifestation, commonly with bilateral involvement.[5] Other presentations of ocular syphilis include optic neuropathy, interstitial keratitis, anterior uveitis and retinal vasculitis.[4,6]

The CDC defines ocular syphilis as clinical symptoms or signs consistent with ocular disease (e.g., uveitis, panuveitis, diminished visual acuity, blindness, optic neuropathy, interstitial keratitis, anterior uveitis, or retinal vasculitis) in patients with syphilis of any stage.[7]

A serologic diagnostic workup for syph-

Known as "the great masquerader," ocular syphilis can occur in nearly any ocular structure as early as six weeks after transmission and may often be the only sign of systemic syphilis.

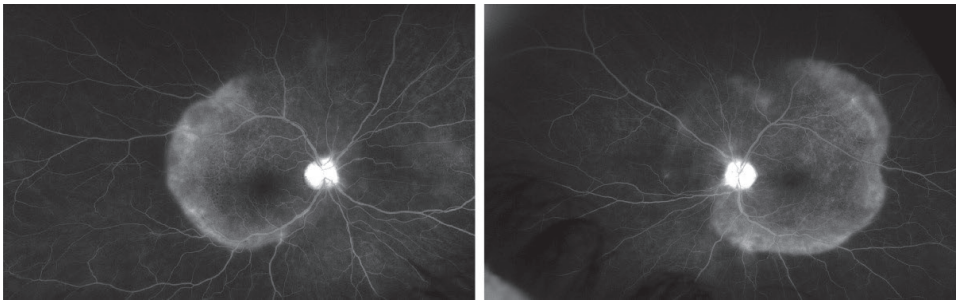

Figure 3. Fluorescein angiogram revealed bilateral hyperfluorescent staining of the placoid macular lesions with irregular hyperfluorescence nasally as well as focal staining along the vessels and disc hyperfluorescence.

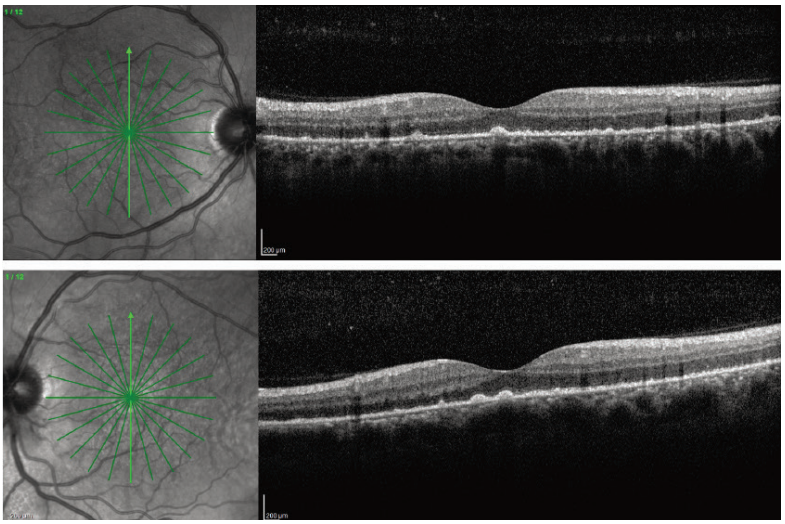

Figure 4. Optical coherence tomography revealed bilateral diffuse outer segment irregularity with disruption of the outer retinal layers and hyperreflective nodular retinal pigment epithelial lesions in a rosary bead pattern.

ilis should be completed either with traditional serologic testing or with reverse screening algorithms.[7]

Traditional serology includes a positive nontreponemal test (e.g., RPR or VDRL) confirmed by a treponemal-specific test (e.g., *Treponema pallidum* enzyme immunoassay or fluorescent treponemal antibody absorption). However, reverse screening algorithms, in which a treponemal test is performed followed by a confirmatory nontreponemal test, are gaining popularity.

In patients with a high suspicion of syphilis despite negative testing, consider a prozone phenomenon, which occurs when extremely high syphilis antibody titers interfere with the serologic test and result in a false-negative test.[8] All patients with a new diagnosis of ocular syphilis should be tested for HIV and screened for other common sexually transmitted diseases, specifically gonorrhea and chlamydia.[7]

Clinical characteristics of ASPPC

J. Donald M. Gass, MD, and colleagues at Bascom Palmer Eye Institute first described acute syphilitic posterior placoid chorioretinitis (ASPPC) in 1990.[9]

ASPPC is defined by the presence of one or more placoid, yellowish, outer retinal lesions, typically involving the posterior pole and the mid-periphery of the retina near the temporal vascular arcade. ASPPC may have a unilateral or bilateral involvement with a presenting visual acuity ranging from 20/20 to no light perception.[10]

OCT to diagnose ASPPC

The advent of OCT imaging has made it possible to report pathognomonic features of ASPPC, which include punctate hyperreflectivity in the choroid, disruption and loss of the ellipsoid zone, nodular irregularity of the retinal pigment epithelium and transient localized subretinal fluid.[11,12]

Although the pathophysiology of ASPPC isn't completely understood, timing and characteristics of spectral-domain OCT findings may reflect the sequence of disease events.[11] Some authors suggest that circulating *T. pallidum* organisms may enter the choroidal circulation and gain access to the outer retina where the choroidal vascular supply is greatest.

This subsequent access to the outer retina may result in impaired photoreceptor function expressed as disruption of ellipsoid zone on OCT. These changes may be secondary to direct invasion of *T. pallidum* organisms from the choroidal

In patients with a high suspicion of syphilis despite negative testing, consider a prozone phenomnon—when extremely high syphilis antibody titers interfere with the serologic test and result in a false-negative test.

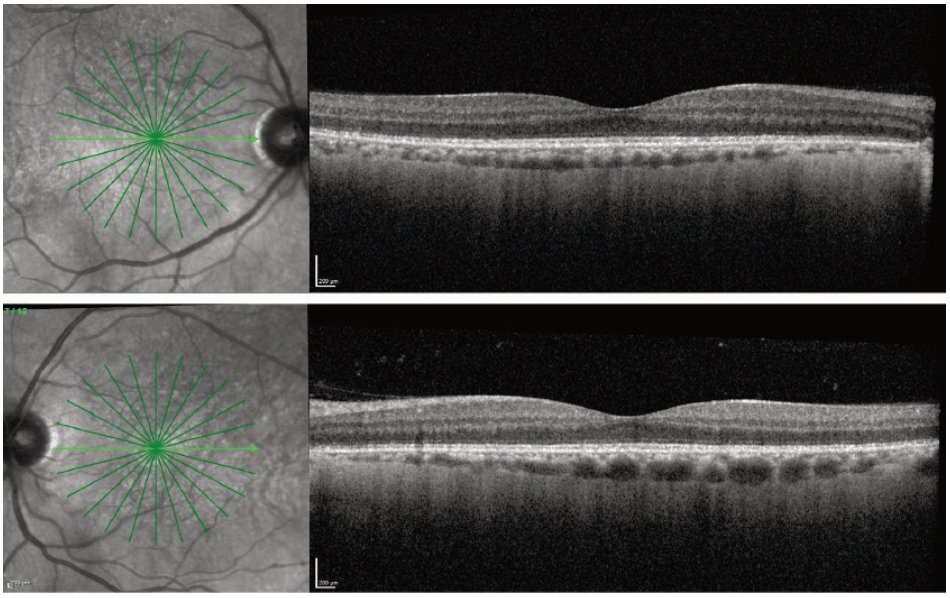

Figure 5. Optical coherence tomography three weeks post-treatment shows reconstitution of the outer retinal layers and disappearance of the hyperreflective nodular lesion.

Sexual partners of patients with ocular syphilis should be notified, and the case should be reported to the local health department.

circulation or secondary inflammation of the choriocapillaris-RPE-photoreceptor complex.[10,12,13]

Treatment

Ocular syphilis should be treated as neurosyphilis with 18 million to 24 million units IV aqueous crystalline penicillin G per day for 10 to 14 days.[7] If cerebrospinal fluid pleocytosis or elevated protein is initially present, the CDC recommends repeated lumbar puncture every six months until the cell count or protein level normalizes.

Sexual partners of patients with ocular syphilis should be notified, and the case should be reported to the local health department.

Bottom line

ASPPC is a subtype of neurosyphilis that requires treatment with intravenous penicillin in consultation with infectious disease specialists. All patients with a new ocular syphilis diagnosis should be tested for HIV and screened for other common sexually transmitted diseases. RS

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"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

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Department Editor *By Akshay S. Thomas, MD, MS*

PPV in the management of uveitis

Pars plana vitrectomy can be an important tool in the diagnosis and treatment of uveitic disease in carefully selected patients.

By Stephen Laswell, Hannah J. Yu, Zane Khademi, MD, and Christopher R. Henry, MD

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DISCLOSURES: Dr. Henry is a consultant for Clearside Biomedical and Bausch + Lomb. Mr. Laswell, Ms. Yu and Dr. Khademi have no relevant disclosures.

Pars plana vitrectomy was first reported as a potential therapeutic tool for patients with uveitis in 1981, demonstrating an improvement in visual acuity in 75 percent of eyes in a series of 28 patients.[1] In the decades since, techniques and technologies have evolved, and PPV has further emerged as an important therapeutic and diagnostic tool in uveitic patients.

As a therapeutic approach, reported benefits of PPV for uveitis include the removal of inflammatory cells and cytokines, the debulking of vitreous opacities and membranes, the repair of associated retinal pathology and the potential to reduce cystoid macular edema.[2,3] Several studies have suggested that PPV may also be helpful in reducing the burden of systemic therapy in select patients with uveitis.[3] Here, we outline current applications of PPV in the diagnosis and treatment of uveitis.

Diagnostic PPV for undifferentiated uveitis

In cases of undifferentiated uveitis, PPV can serve as a valuable diagnostic tool to identify infection, detect malignancy and explore potential alternative diagnoses. Biopsy samples obtained during PPV to assess for underlying pathology typically include undiluted vitreous, diluted vitreous and the vitreous cassette samples (*Figure 1*). Working with a dedicated ocular pathologist is particularly helpful to differentiate the infectious, autoimmune or malignant ophthalmic processes.

In cases of suspected infection, standard stains and cultures are performed for bacteria, fungus and mycobacterium. Additionally, multiplex polymerase chain reaction (PCR) test may be ordered to detect herpes simplex virus 1 or 2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus and toxoplasmosis, among others.

If needed, bacterial, fungal and acid-fast bacilli DNA sequencing can be obtained through labs such as at the University of Washington. In cases of suspected malignancy, molecular genetics, immunohistochemistry and flow cytometry may be indicated.

Cytology may also be beneficial in cases of autoimmune uveitis to distinguish granulomatous vs. non-granulomatous inflammation, an important distinction for determining the etiology of ocular inflammation.

In four recent studies evaluating PPV in

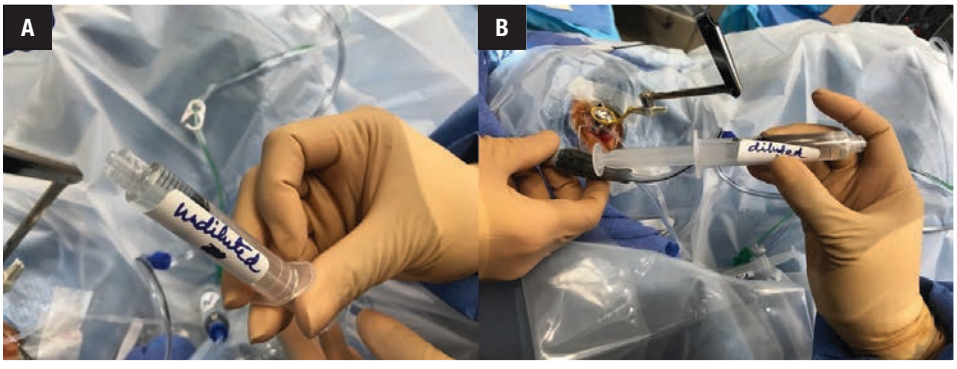


Figure 1. Vitreous humor samples from a uveitic patient receiving diagnostic pars plana vitrectomy. Undiluted (A) and diluted (B) samples of the vitreous humor are collected during vitrectomy and sent for analysis to aid in diagnosis. The vitreous cassette and aqueous humor may also be sent for analysis.

uveitis, a definitive diagnosis was established in 20 to 60 percent of cases. Aggregating the results of these studies, vitreous biopsies provided the diagnosis in 34 percent (85/248) of undifferentiated eyes, returning positive for such conditions as endogenous mycosis (31 eyes), lymphoma (21 eyes), toxoplasma chorioretinitis (10 eyes), HZV and/or acute retinal necrosis (10 eyes), benign neoplastic masquerades (six eyes) and other miscellaneous infections (seven eyes).[3–7]

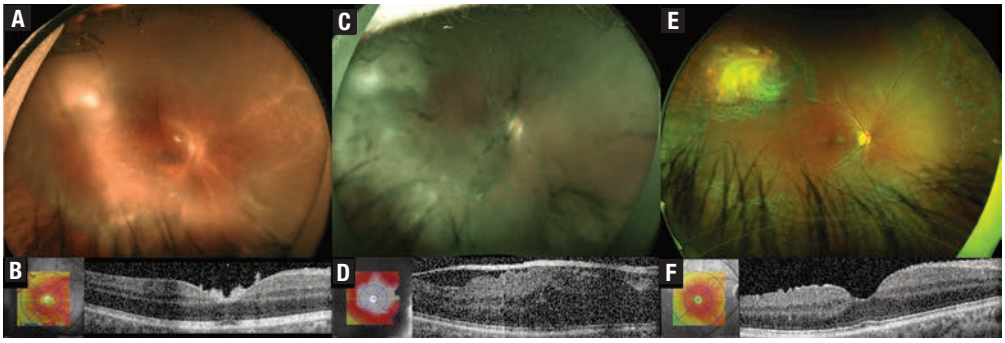


Figure 2. Fundus photography from a 40-year-old male with panuveitis due to toxoplasma chorioretinitis OD. The patient presented at baseline (A and B) with vitreous opacities, retinal whitening and vascular sheathing with 20/400 vision. The patient was prescribed systemic antibiotics (clindamycin and sulfamethoxazole/trimethoprim) and oral corticosteroids. At the five-month follow-up (C and D), the infection resolved, but persistent vitreous opacities and hemorrhage, epiretinal membrane, and cystoid macular edema remained. The patient's vision remained 20/400. The patient was intolerant of further systemic corticosteroids and, therefore, elected to undergo pars plana vitrectomy. At three months postoperatively (E and F), the patient had complete resolution of previous vitreous and retinal pathology and vision improved to 20/20.

Therapeutic PPV in uveitis

PPV also serves a therapeutic role for certain uveitic patients. Although indications for therapeutic PPV in the setting of uveitis are broad and varied, studies have reported meaningful improvements in anatomic and visual outcomes, along with the potential for reduction in the need for systemic treatment.

A systematic review of PPV for uveitis from 2005 to 2014 reported improved CME, enhanced visual acuity and reduced need for corticosteroids and immunomodulatory therapy following PPV.[3] In this review, 69 percent of uveitic eyes demonstrated improved VA compared to 13 percent with worsening VA following PPV. Additionally, 14 of 16 studies demonstrated a reduction in the percentage of patients with CME. Meanwhile, median use of systemic corticosteroids decreased from 48 percent preoperatively to 12 percent postoperatively and median use of systemic immunomodulatory drugs decreased from 56 percent preoperatively to 36 percent postoperatively.

Additional studies have examined the efficacy of PPV in infectious uveitis. In a study from India of patients with bilateral posterior uveitis due to ocular tuberculosis, eyes undergoing PPV had improved control of ocular inflammation at postoperative months one and three (74 percent and 97 percent) compared to non-PPV eyes (20 percent and 83 percent), in addition to more significant improvement in best-corrected VA.[9]

Vitrectomy has also been reported to improve visual outcomes when performed for persistent vitreous inflammation in cases of recalcitrant ocular toxocariasis.[10] Similarly, a few recent manuscripts reported PPV to be an effective option to improve vision for both visually significant ocular toxocariasis- and toxoplasmosis-related epiretinal membranes and macular holes.[10-12]

Vitrectomy is a therapeutic option for certain cases of acute retinal necrosis (ARN), though results are more varied considering the aggressive nature of this condition and its generally poorer prognosis. Studies investigating the role of early PPV in patients with ARN have suggested

(Continued on page 17)

Pearls for foreign body removal

The fine art of using internal and external magnets to extract magnetic foreign bodies.

By Harris Sultan, MD, MS, and Rajendra Apte, MD, PhD

Harris Sultan, MD, MS

Rajendra Apte, MD, PhD

Intraocular foreign bodies can result in potential complications of endophthalmitis, retinal detachment, vitreous hemorrhage and other metal-based toxicities such as siderosis (due to the presence of iron) or chalcosis (due to the presence of copper).

Moreover, surgical removal of foreign bodies can often be challenging because the foreign bodies themselves can be difficult to grasp and extract. Here, we describe a few pearls in the removal of a magnetic intraocular foreign body.

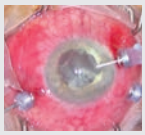
Hemostasis at the time of foreign body removal

An intraocular foreign body may be found at various levels in the posterior segment ranging from intravitreal to trans-scleral. If it involves the choroid, the foreign body may be providing a vascular tamponade, keeping the choroidal vasculature from bleeding.

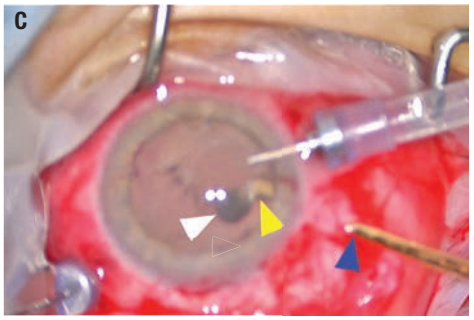
The removal of a trans-choroidal foreign body can result in significant intraoperative hemorrhage. Increasing the infusion pressure to 80 mmHg at the time of foreign body removal may help reduce choroidal hemorrhage.

Additionally, we apply laser and/or diathermy around the insertion of the IOFB to help coagulate surrounding retinal vessels. Sometimes, blunt tamponade with intraocular instruments—for example, a

View the Video



Watch as Drs. Sultan and Apte demonstrate the use of magnets to extract intraocular foreign bodies.
http://bit.ly/VideoPearl_019



An intraocular rare-earth metal magnet (A) has a 20-gauge shaft that can retrieve magnetic foreign bodies. A conjunctival cut-down and enlargement of a pre-existing sclerotomy is generally needed to use these magnets. Applying pressure to the lever of the device will expose the magnetic-portion (B, blue arrowhead) at the tip of the shaft. The magnet enters the sclerotomy (C, blue arrowhead) and the tip (yellow arrowhead) makes contact with the magnetic foreign body (white arrowhead). The magnet may be used to bring the foreign body anteriorly for eventual removal with forceps either through an enlarged corneal wound (shown here) or scleral wound.

Bios

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DISCLOSURES: Drs. Sultan, Apte and Hahn have no relevant financial disclosures.

light pipe or the tip of the vitreous cutter—can be helpful if bleeding persists.

Use of magnets

Both internal and external magnets can be helpful in extracting magnetic foreign bodies. An internal magnet is a rare-earth magnet that attracts ferro-magnetic objects towards its typically 20-gauge shaft. To introduce the internal magnet, perform a conjunctival cut-down and use a 20-gauge micro-vitreoretinal blade to create or enlarge a sclerotomy.

An internal magnet is helpful when other tissues, including retina, choroid and vitreous, encapsulate the foreign body. The magnet provides a controlled amount of force for dissecting the foreign body from surrounding tissues. The internal magnet can then extract the foreign body in a controlled fashion, often requiring the assistance of external forceps to extract the foreign body.

Although less commonly available, an external magnet may be helpful to draw unencapsulated foreign bodies to an extraction site. Place the external magnet at the site of the enlarged sclerotomy and activate it once it's properly positioned.

If the foreign body is lodged under the retina, choroid or extensive vitreous, the powerful external magnet may pull it through these tissues and result in complications such as retinal detachment and hemorrhage, so use it judiciously.

Bottom line

Removal of intraocular foreign bodies can sometimes be challenging. In these cases, internal or external magnets may be a helpful part of a vitreoretinal surgeon's armamentarium. RS

PPV for uveitis

(Continued from page 15)

it may lower rates of ARN-associated rhegmatogenous retinal detachments, but a definitive role in prevention is still unclear.[13,14]

Clinical case study

An otherwise healthy 40-year-old man presented to the clinic with panuveitis in the right eye of several months duration and BCVA of 20/400. Imaging showed evidence of severe vitreous debris, an active superotemporal chorioretinal lesion, and profound vascular sheathing (*Figure 2A, page 15*). The suspected etiology was toxoplasma chorioretinitis, confirmed by anterior chamber PCR and positive serologies. We prescribed an extended course of oral clindamycin and sulfamethoxazole/trimethoprim, in conjunction with a tapered course of prednisone.

At the five-month follow-up visit, the infection had regressed and the chorioretinal lesion was consolidated and inactive. However, the patient had persistent vitreous opacities and hemorrhage in addition to a prominent epiretinal membrane (*Figure 2C, page 15*). The patient also could not tolerate the side effects of a prolonged course of systemic corticosteroids.

Due to the persistent vitreous debris and inability to continue steroids, the patient accepted the option of PPV with membrane peeling. In the meantime, he was continued on maintenance sulfamethoxazole/trimethoprim every Monday, Wednesday and Friday to prevent reactivation of infection.

At three months post-PPV, the patient had complete resolution of vitreous debris, haze, retinal edema, and epiretinal membrane with improvement of VA to 20/20 (*Figure 2E, page 15*). At six months post-PPV, the patient had stable vision without recurrence of chorioretinitis, vitritis or epiretinal membrane.

Bottom line

PPV can play an important role in the management of uveitis as both a diagnostic and therapeutic tool. Patient selection is critical, but in appropriate patients, don't overlook the use of PPV in the management of uveitis. RS

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Signature OCT findings as a diagnostic tool

How imaging helped diagnose neurofibromatosis type 1, retrograde trans-synaptic degeneration, bacillary detachment and photothermal injury.

By Juliet Essilfie, MD, and Yasha Modi, MD


Juliet Essilfie, MD


Yasha Modi, MD

Take-home points

- A multifocal hyperreflective lesion on near-infrared imaging that localizes to the choroid is diagnostic of neurofibromatosis type 1.
- Homonymous thinning of the retinal ganglion cell layer should make you think of retrochiasmal central-nervous-system pathology because it highlights retrograde trans-synaptic degeneration.
- Photoreceptor layer splitting detachment, otherwise known as a bacillary detachment, is typically suggestive of a choroidopathy.
- A child that presents with acute vision change in the setting of focal outer retinal tissue loss and an otherwise unremarkable ocular exam should be questioned about a history of laser pointer exposure.

Bios

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Dr. Modi is a retina and uveitis specialist and an assistant professor of ophthalmology at NYU Langone Health.

Disclosures: Dr. Essilfie has no financial relationships to disclose.

Dr. Modi serves as a consultant to Alimera, Allergan (AbbVie), Novartis and Zeiss.

Spectral-domain optical coherence tomography is an essential tool for today's practicing ophthalmologist. Most clinicians have come to rely on SD-OCT for the management and prognostications of various retinal pathologies, particularly diabetic macular edema, age-related macular degeneration and retinal vein occlusion, among other diseases.

However, beyond its ability to help with management and prognostication, OCT can play a significant role in the diagnostic process as well. In this article, we describe cases with "signature" OCT findings that helped lead us to the diagnosis.

All patients presented here were evaluated in the retina division of New York University Medical Center. This report is in accordance with the ethical standards of the Declaration of Helsinki.

Case 1: Choroidal neurofibromatosis

A 16-year-old girl presented for a routine eye exam and new glasses. She had no visual complaints and her best-corrected vision was 20/20 in both eyes. Near-infrared imaging of the macula demonstrated multiple hyperreflective round-to-ovoid lesions scattered throughout the posterior pole with corresponding cross-sectional B scans, localizing these lesions to the choroid (*Figure 1*).

Once considered a rare form of neurofibromatosis, choroidal neurofibromatosis was typically identified in post-mortem examinations due to difficulty visualizing the nodules with conventional ophthalmoscopy.

In 2000, researchers in Japan reported on the presence of bright patches on near-infrared imaging of the posterior pole of neurofibromatosis type 1 (NF1) patients that correlated with hypofluo-

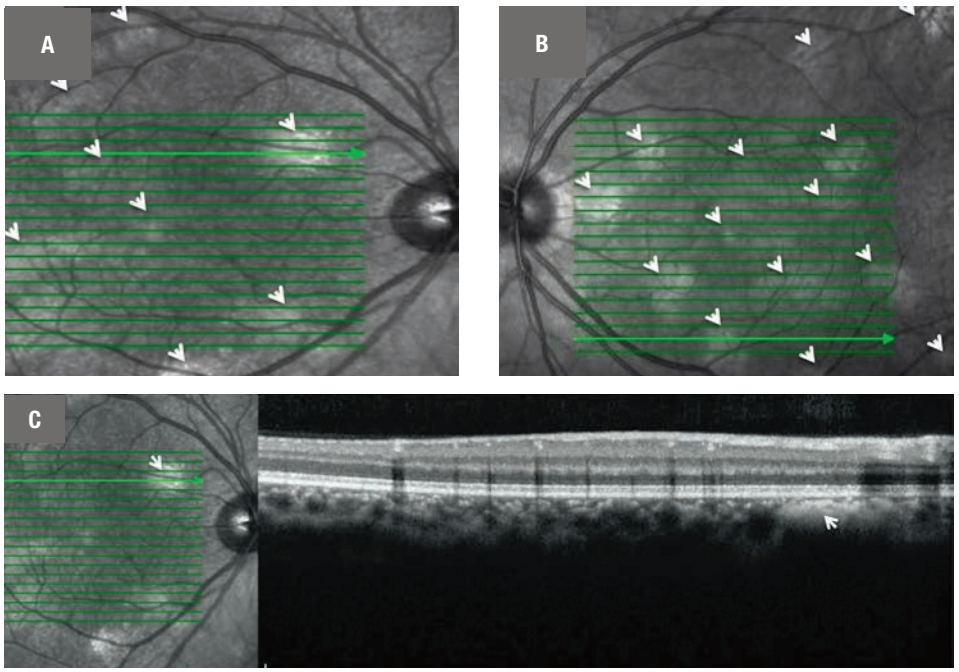

Figure 1. Near-infrared imaging of the right and left eyes (A, B) with multiple bright round-to-ovoid lesions (arrows) within the macula. These lesions localize to the choroid on cross-sectional optical coherence tomography (C, arrow) and demonstrate compression of the choriocapillaris with a homogeneous hyperreflective signal in Sattler and Hallers layer.

rescent regions on indocyanine-green angiography.[1] Since then multiple publications have described the presence and prevalence of choroidal neurofibromatosis using OCT.[2,3]

Researchers at the University of Milan found that when using near-infrared imaging, choroidal neurofibromas were identified in up to 82 percent of NF1 eyes. Diagnostic accuracy increased to 90 percent in the general population when a cutoff of 1.5 nodules was used.[3] In contrast, Lisch nodules and optic gliomas have a prevalence of 72 percent and 6 percent, respectively, in adult and pediatric patients combined.[3]

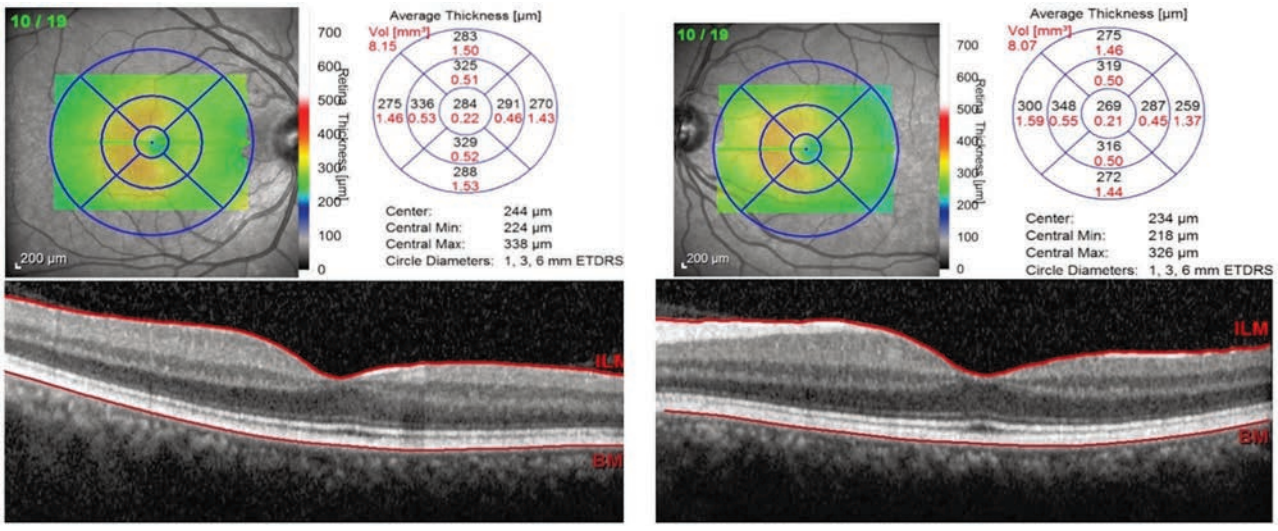

Figure 2. While the cross-sectional imaging of the optical coherence tomography scan looks "normal," the volumetric analysis of the OCT highlights mild thinning of the nasal macula OD and the temporal macula OS. The color-coded analysis helps to bring out this micron-level change where the thin retina appears green on the map relative to the normal orange color that typifies normal parafovea.

Despite their higher clinical prevalence, the diagnostic criterion for NF1 has yet to be updated to include choroidal neurofibromas. Nevertheless, the presence of bright lesions on near-infrared that correspond to hyperreflective choroidal lesions on OCT scans is a signature of NF1 (but not NF2), and should prompt further systemic exam to confirm the diagnosis. This case highlights the ability of OCT to aid in both phenotypic and genotypic diagnosis.

Case 2: Retrograde trans-synaptic degeneration

A 37-year-old man with a history of HIV and hemophilia presented for routine eye exam. Best-corrected visual acuity was 20/20 in both eyes. Slit lamp exam of the anterior and posterior segment was within normal limits.

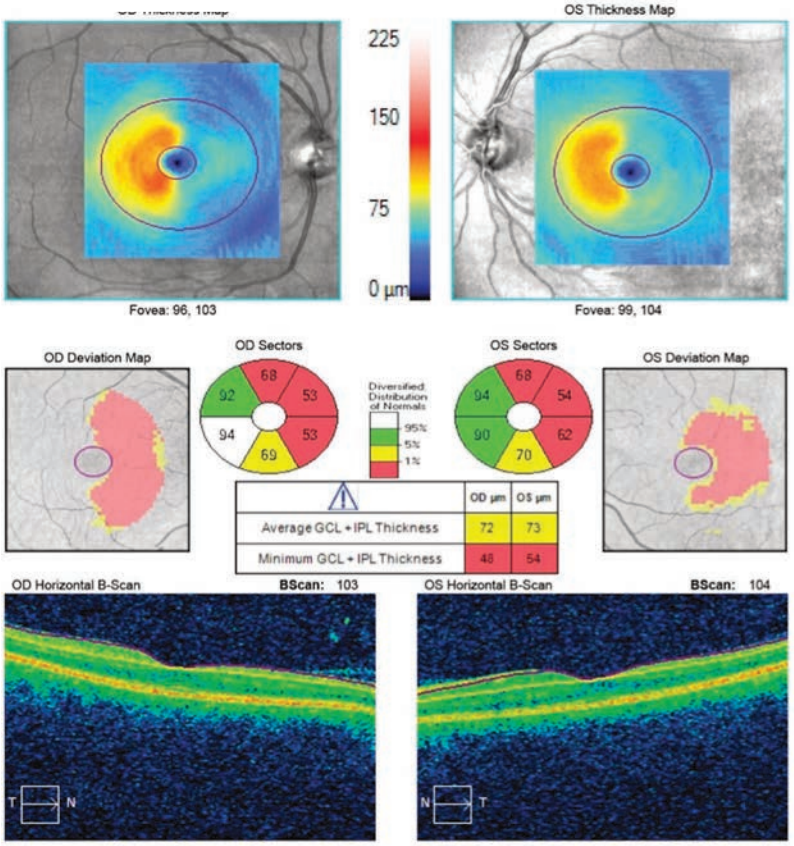

Figure 3. Segmentation of the optical coherence tomography scan to isolate the ganglion cell-inner plexiform layer thickness demonstrates nasal macular ganglion cell loss OD and temporal macular ganglion cell loss OS.

Volumetric analysis of the OCT demonstrated slight thinning of the right nasal and left temporal macula respecting the vertical raphe (*Figure 2, page 19*). While OCT of the retinal nerve fiber layer was normal, OCT analysis of the retinal ganglion cell layer (GCL) confirmed marked thinning of the ganglion cell and inner plexiform layer in the same region (*Figure 3*).

A 24-2 Humphrey Visual Field confirmed a dense right homonymous hemianopia (*Figure 4*). Further history taking revealed that the patient had a history of spontaneous cerebral hemorrhage as a toddler, which led to his ultimate diagnosis of hemophilia.

Severe injury to the nerve fibers within the visual cortex can result in nerve function loss. When this loss of function progresses toward the synapse to the presynaptic cell, this process is termed retrograde trans-synaptic degeneration (RTSD) of the retinal ganglion cell.[4,5] One hypothesis is that this occurs due to the presynaptic dendritic tree no longer supplying trophic support to the injured cell.[4]

While RTSD was originally thought to occur in a "critical" window in early childhood or sooner, OCT imaging has identified cases in adults.[5]

In this case, segmentation algorithms in OCT analysis identified the loss at the GC-inner plexiform layer (IPL). It's important to realize that an OCT of the RNFL, however, would be normal because the nerve fiber layer doesn't degenerate in these cases.[6]

If OCT demonstrates volumetric loss of tissue in a homonymous pattern, consider GC-IPL analysis and visual field perimetry for confirmation of homonymous hemianopsia—a marker of brain injury that may warrant systemic management. After all, we are retinal specialists and the OCT precedes all else!

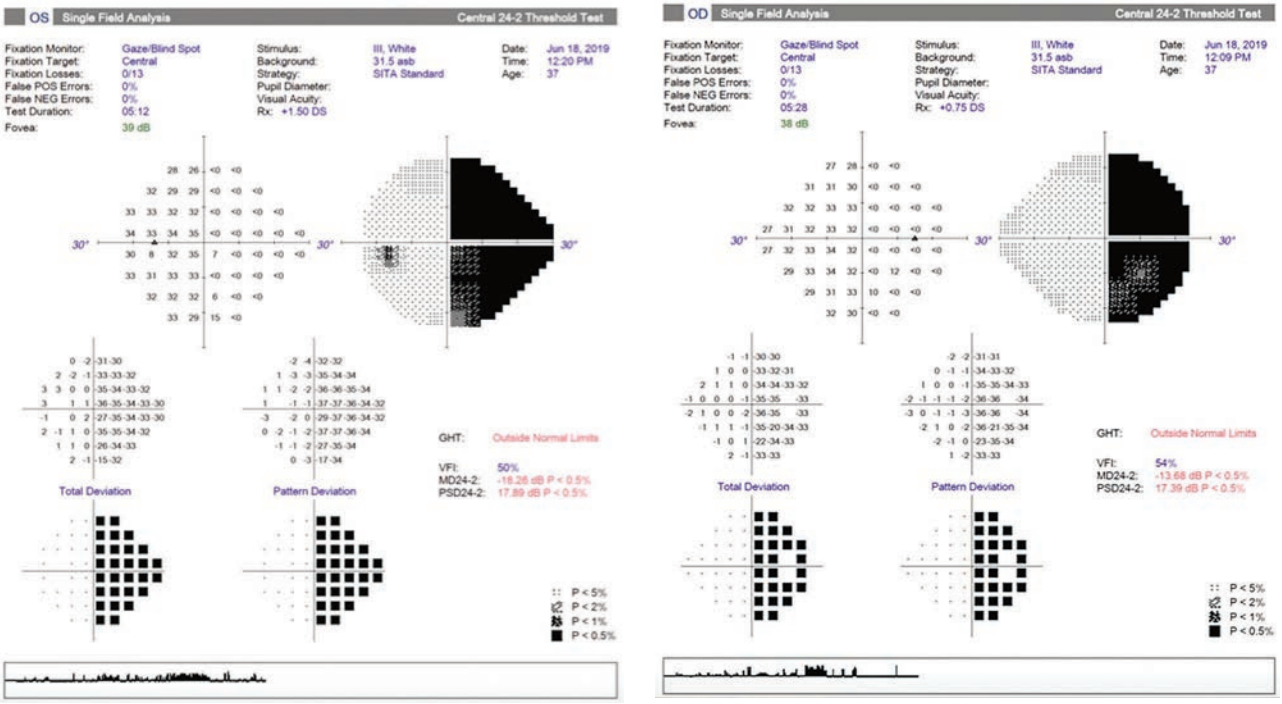

Figure 4. 24-2 Humphrey Visual Field demonstrates a dense right homonymous hemianopia that corresponds to the inverse of the ganglion cell layer loss seen in Figure 3 (right visual field loss and left-sided macular ganglion cell loss).

Case 3: Bacillary detachment

A 33-year-old man with a history of toxoplasmosis chorioretinitis presented with blurry vision and floaters in the right eye for one week. BCVA of the right eye was 20/200. Fundus exam demonstrated mild vitritis with a cluster of full thickness retinal whitening adjacent to a small hyperpigmented scar (*Figure 5*).

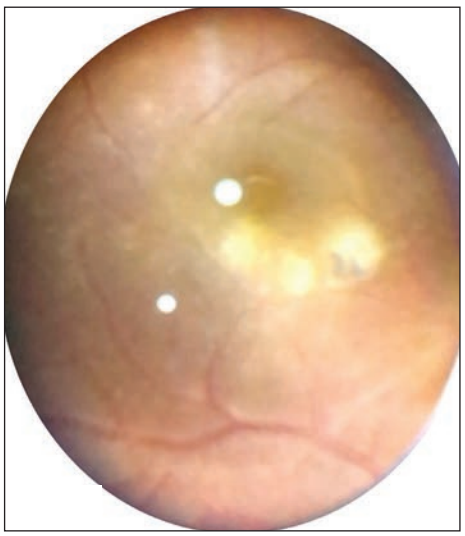

Figure 5. Color fundus photography demonstrates typical chorioretinitis adjacent to a small hyperpigmented scar within the macula, is a classic feature of toxoplasmosis chorioretinitis.

OCT of the macula illustrated a dome-shaped photoreceptor layer splitting detachment (*Figure 6, page 22*). Both the chorioretinitis and detachment resolved after treatment with antibiotics and steroid for one month.

OCT characterized the bacillary detachment, referencing this dome-shaped photoreceptor splitting, as a large cystic space within the outer retina that had hyperreflective material along the outer retinal surface and a thin band at its base that appeared continuous with the adjacent ellipsoid band or external limiting membrane.[7] It's theorized that the cystic space is located at the level of the photoreceptor inner segment myoid.[7]

Bacillary detachments have been reported in several other etiologies, most of which involve a compromise in the choroidal health. These etiologies

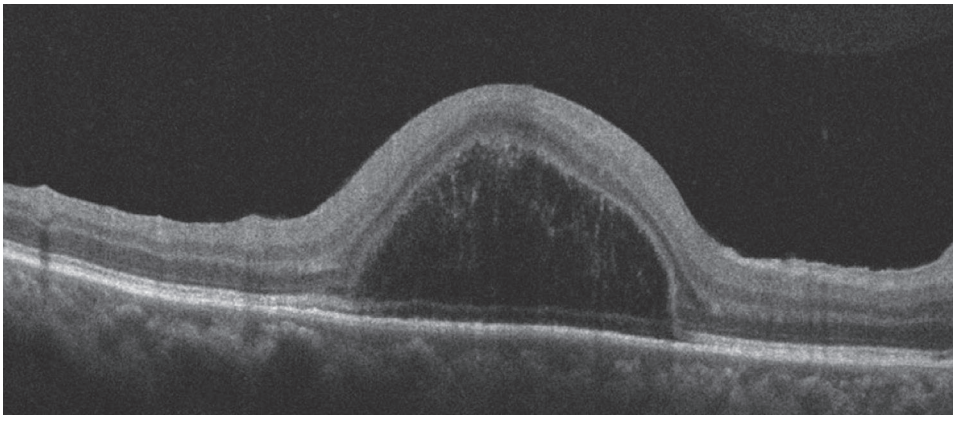

Figure 6. Optical coherence tomography of the macula demonstrates a bacillary detachment (a photoreceptor-splitting detachment). Note the hyperreflective material along the outer retinal surface. A thin band at the base of the cystic detachment is continuous with the adjacent ellipsoid band and external limiting membrane.

include central serous chorioretinopathy, Vogt-Koyanagi-Harada disease, adjacent-to-fibrovascular pigment epithelial detachments in exudative AMD, choroidal rupture and acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[8] So the presence of a bacillary detachment on OCT is useful in narrowing the differential diagnosis to a potential choroidopathy.

The presence of bacillary detachment on optical coherence tomography is useful in narrowing the differential diagnosis to a potential choroidopathy.

Case 4: Photothermal damage

An 8-year-old boy with type 1 diabetes presented with blurry vision in the right eye for the past two years. BCVA of the right eye was 20/80. Anterior segment exam was within normal limits. Fundoscopy was notable for a streak-like yellow foveal lesion (*Figure 7*).

Near-infrared OCT imaging revealed multiple tightly clustered, small bright round foveal lesions (*Figure 8*). OCT of the macula illustrated multiple focal areas of ellipsoid zone disruption corresponding to the bright lesions on infrared. The pattern of focal EZ loss was consistent with thermal injury from a laser pointer. The parents agreed that both the patient and his sister had laser pointers at home.

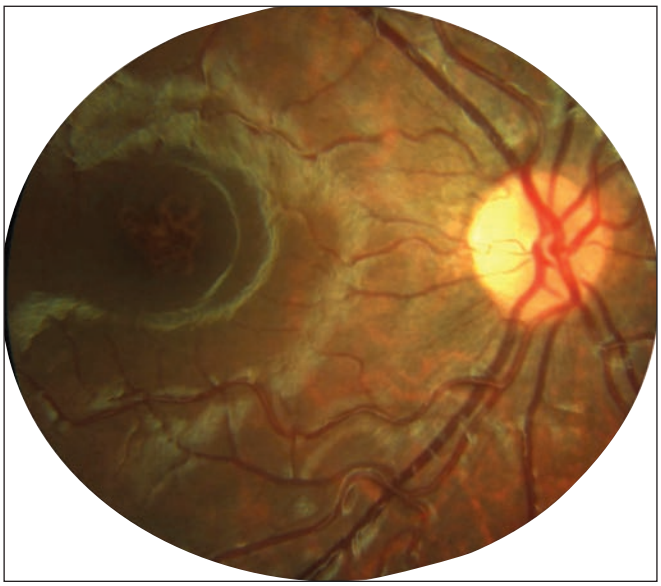

Figure 7. Fundus photograph of the right macula shows a whorl-like yellow foveal lesion.

Ocular exposure to laser pointers can cause photothermal damage to the retina. Retinal injuries range from photoreceptor disruption to

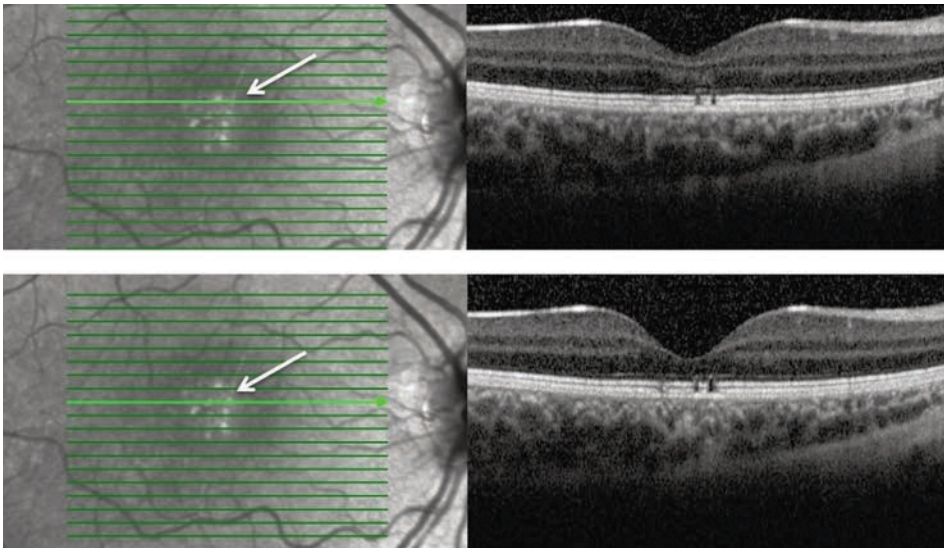

Figure 8. Near-infrared imaging on the left demonstrates multiple small hyperreflective spots as well as bright streaks (arrows). These bright areas correspond to focal ellipsoid zone loss on optical coherence tomography. Focal areas of choroidal hypertransmission localizing to the EZ loss are consistent with retinal pigment epithelium atrophy.

photoreceptor and RPE disruption to full thickness macular holes.[9] In the acute setting, OCT may demonstrate vertical or oblique lines of hyperreflectivity extending from the outer nuclear layer to the RPE. With time this hyperreflectivity can resolve, leaving behind focal outer retinal tissue loss.

Streak lesions are suggestive of self-inflicted laser pointer misuse, while focal lesions are suggestive of accidental or third-party-induced injury.[9,10] Visual impairment can be transient or permanent depending on the intensity and duration of laser exposure. As the streak-like macular lesions suggested, our patient later admitted to a history of pointing a laser pen toward his right eye.

Bottom line

OCT imaging has indeed established its role in the management and prognostication of various retinal diseases. As we discussed here, it has the added benefit of illustrating signature findings that may aid in narrowing the differential diagnosis. While some of the findings may be subtle at first glance, these OCT features will hopefully remain indelibly in our memories for later recollection when a similar mystery patient presents. RS

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Streak lesions are suggestive of self-inflicted laser-pointer misuse, while focal lesions are suggestive of accidental or third-party-induced injury.

Understanding role of Ang2 in neovascular AMD

Angiopoietin-2 is an increasingly desirable target in age-related macular degeneration. Here's why, and an assessment of investigative treatments.

By Eric Williams, MD, Matthew Powers, MD, MBA, and Jeffrey Olson, MD

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Bios

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Disclosures: Drs. Williams and Powers have no relationships to disclose. Dr. Olson holds equity in Front Range Ophthalmics, 2C Tech and AmpVision.

Take-home points

- Angiopoietin-2 (Ang2) is a key molecule in the angiogenesis pathway and is directly involved in the Angiotensin-1 (Ang1)/Tie2 signaling axis.
- Animal models have shown that Ang2 inhibition leads to decreased vascular permeability, and dual inhibition of Ang2 and vascular endothelial growth factor leads to a significant reduction in vascular permeability greater than inhibition of either Ang2 or VEGF alone.
- Faricimab, a bispecific monoclonal antibody to Ang2 and VEGF-A, has demonstrated noninferiority in both 16- and 12-week injections to ranibizumab every four weeks.
- Nesvacumab, a monoclonal antibody that inhibits Ang2, in combination with aflibercept was found to be equivalent in efficacy to aflibercept alone.

The discovery of anti-vascular endothelial growth factor and its effects on the pathogenesis of neovascular age-related macular degeneration drastically altered our treatment paradigm and the prognosis of patients.[1] However, multiple studies suggest other pathways also contribute to pathologic angiogenesis.

In clinical practice, a substantial portion of patients still don't respond to anti-VEGF monotherapy with bevacizumab or ranibizumab (Avastin and Lucentis, Genentech/Roche).[4] Moreover, in the VIEW1 and VIEW2 studies, even though 95 percent of nAMD patients maintained their vision, only approximately 30 percent had an improvement of 15 or more letters in best-corrected visual acuity.[2,3]

The angiogenesis pathway

Angiopoietin-2 (Ang2) is a key molecule in the angiogenesis pathway and is directly involved in the Angiotensin1 (Ang1)/Tie2 signaling axis. Ang2 is produced almost exclusively by endothelial cells and functions as a vessel-destabilizing molecule through its competition with Ang1 and inhibition of Tie2.[6] The central role of Ang2 in the angiogenesis cascade has led to intense exploration for the development of anti-angiogenic drugs in ophthalmology and across other specialties.[7-9]

Similar to VEGF, Ang2 is upregulated by hypoxia, and ocular levels of both Ang2 and VEGF are elevated in eyes with nAMD. Additionally, multiple studies have demonstrated that VEGF and Ang2 are co-regulated in proangiogenic disease states and may also work together to induce pathological neovascularization and increased vascular permeability.[10-14]

These results seem to indicate that not only will inhibiting Ang2 provide therapeutic benefit in the treatment of nAMD,

but combined inhibition of VEGF and Ang2 may produce a greater effect than either one individually.

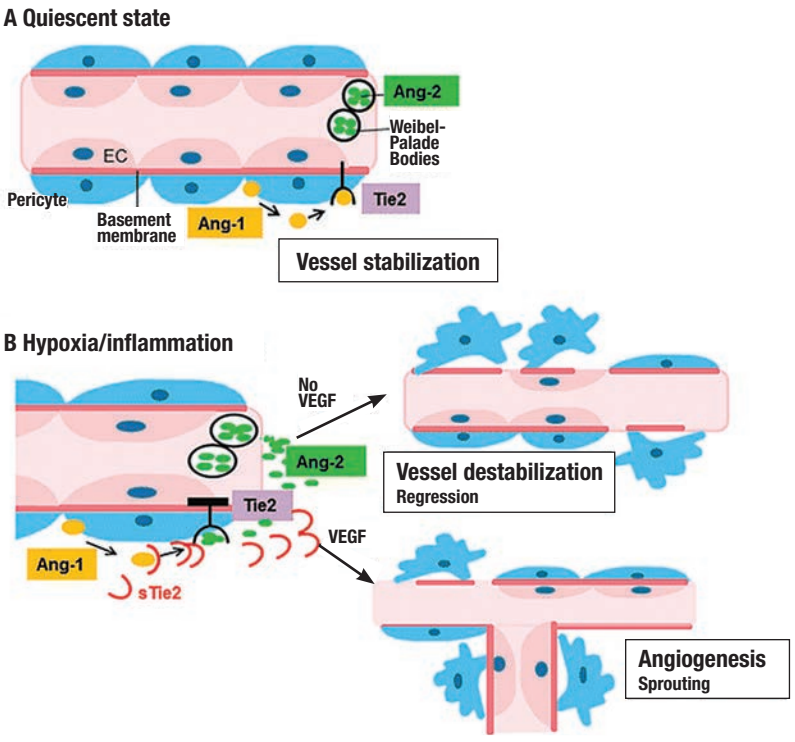
Breakthrough Ang2 research

In 2016, researchers in Europe tested this theory of improved therapeutic benefit of combined inhibition of VEGF and Ang2.[15] Utilizing a mouse model of aberrant retinal angiogenesis, they demonstrated that dual inhibition of VEGF-A and Ang2 significantly reduced vascular leakage when compared to not just controls, but also when compared to either Ang2 or VEGF inhibition alone.

The same team went on to design the first bispecific monoclonal antibody designed for the eye that binds to and inactivates VEGF-A and Ang2. RG7716 (now known as faricimab, Genentech/Roche) was first tested on non-human primates in a laser-induced CNV model. They compared faricimab to the anti-VEGF-A Fab fragment ranibizumab alone and anti-Ang2 alone, and found that treatment with faricimab significantly reduced the amount of vessel leakage demonstrated on fluorescein angiography, and also reduced retinal architecture distortion.[15]

The Phase I trial of faricimab enrolled 24 patients with nAMD and refractory subfoveal choroidal neovascularization (leakage on FA or fluid on optical coherence tomography despite three or more intravitreal anti-VEGF treatments) who received single intravitreal doses of 0.5 mg, 1.5 mg, 3 mg and 6 mg of faricimab in a stepwise dose-escalation manner.[16]

Faricimab was tested in a multiple-dose phase where six patients received three treatments each of 3 mg and 6 mg. No dose-limiting toxicities were reported in either group; only one patient withdrew and one serious adverse event occurred (both of which were deemed to be unrelated to the study drug). Even in this small trial, both the stepwise dose-escalation group and the multiple-dose group had a median improvement in BCVA of at least 7 letters.



The role of angiopoietins and Tie2 in vascular biology. In the quiescent state (A), Ang1, produced by pericytes, acts in a paracrine manner on the membrane-bound (mb) Tie2 receptor on endothelial cells (EC). The effects of Ang1/Tie2 signaling ensure vessel stabilization. Ang2, produced by EC, is stored in Weibel-Palade bodies. In hypoxia and inflammation (B), Ang2 is released from the Weibel-Palade bodies and acts in an autocrine manner on EC. Due to competitive binding to mbTie2, Ang2 antagonizes Ang1 signaling. In the absence of vascular endothelial growth factor, the inhibition of Tie2 signaling leads to vessel destabilization and regression due to apoptosis of EC, loss of pericyte coverage and disruption of the basement membrane. In the presence of VEGF, Ang2 exerts pro-angiogenic effects with proliferation and migration of EC and sprouting of new branches. Additionally, VEGF causes shedding of Tie2. sTie acts as a competitive ligand for Ang1/2, thereby blocking downstream signaling with anti-angiogenic effects. (*Used with permission: Moritz F, et al. Tie2 is a novel key factor of angiopathy in systemic sclerosis. Arth Res Ther. 2017;19:105*)

Faricimab Phase II trials

Two Phase II studies recently evaluated faricimab in nAMD. AVENUE[17] is a proof-of-concept study that evaluated the effect of faricimab in patients with choroidal neovascularization secondary to AMD. AVENUE enrolled 273 patients in a multicenter, randomized, comparator-controlled parallel-group clinical trial to evaluate faricimab injections at four- and eight-week intervals (1.5 and 6.0 mg doses) vs.

Ang2 plays a clear role in angiogenesis through its inhibition of the Tie2 signaling pathway. Upregulation leads to pathological angiogenesis, both independently, and through additive effects with VEGF.

ranibizumab (0.5 mg) at four-week intervals in patients with nAMD. At 36 weeks, the study met its non-inferiority outcomes for vision and central retinal thickness.

STAIRWAY[18] was a second Phase II study that evaluated the safety and efficacy of faricimab intravitreal injections at 16- (q16) and 12-week (q12) intervals in patients with nAMD compared to injections of ranibizumab every four weeks. Patients were treated with four loading doses of faricimab 6 mg at four-week intervals, and then were randomized into either q12 or q16 treatment intervals. At week 24 (12 weeks after the last of the four loading doses of faricimab), 65 percent (36/55) of patients treated with faricimab had no active disease.

In STAIRWAY, the following predefined criteria determined disease activity:

- increase in central subfield thickness on SD-OCT >50 µm vs. average over the prior two visits;
- increase in CST ≥75 µm vs. lowest over the prior two visits;
- decrease in BCVA due to nAMD of ≥5 letters vs. average over the prior two visits;
- decrease in BCVA due to nAMD of ≥10 letters vs. highest BCVA over the prior two visits;
- presence of new macular hemorrhage due to nAMD; or
- investigator opinion of significant nAMD disease activity at week 24 requiring immediate treatment.

Additionally, initial improvements in BCVA (11.42, 10.08 and 9.59 letters gained in the q16 and q12 faricimab, and ranibizumab groups, respectively) were maintained in both the q16- and q12-week treatment groups.

CST was similar across all groups at 52 weeks (-122.5 µm, -138.5 µm and -129.9 µm in the q16- and q12-faricimab, and ranibizumab groups, respectively). No new safety signals were observed. The rates of ocular and systemic adverse events with faricimab were similar to ranibizumab.

Additional faricimab trials

Faricimab is being further evaluated for nAMD in two current Phase III trials funded by Genentech/Roche: TENAYA[19] and LUCERNE.[20] These identically designed, multicenter, randomized, double-masked, comparator-controlled studies aim to evaluate the efficacy, safety and durability of faricimab vs. aflibercept (Eylea, Regeneron Pharmaceuticals) in nAMD.

Between the two studies, almost 1,300 patients with nAMD will be randomized to receive either faricimab dosed at q16-week intervals (with the option of decreasing to q12 or q8 weeks), or aflibercept q8 weeks. The primary endpoint for both studies is change in BCVA at 48 weeks compared to baseline. Both studies, as of this writing, are fully recruited with an estimated primary completion date next year.

Faricimab is also being evaluated in the treatment of diabetic macular edema. Like the Phase III nAMD trials, YOSEMITE[21] and RHINE[22] are identical Phase III trials evaluating the efficacy of faricimab in the treatment of DME compared to aflibercept.

Nescvacumab

Regeneron is developing a second experimental monoclonal antibody, nesvacumab. Unlike faricimab, nesvacumab binds to and inhibits only Ang2. A Phase I, open-label, dose-escalation study evaluated the safety of intravitreal REGN910-3 (nesvacumab and intravitreal aflibercept injection [IAI]) in patients with either nAMD or diabetic macular edema.[23] The two highest doses in this trial—REGN910-3 low-dose [3mg:2mg] and REGN910-3 high-dose [6mg:2mg]—were both well tolerated.

ONYX,[24] the primary objective of which was to compare the efficacy of intravitreal REGN910-3 and IAI, was a Phase II, randomized, double-masked study in patients with nAMD. Results didn't show sufficient differentiation between REGN910-3 and aflibercept alone. The aflibercept results

in this study were consistent with findings from earlier clinical studies. Because of these findings, Regeneron announced the Phase III trial wouldn't proceed after the Phase II results were released. In addition to ONYX, a similar study evaluating REGN910-3 in patients with DME, called RUBY,[25] similarly showed insufficient differentiation from aflibercept alone.

Bottom line

Ang2 plays a clear role in angiogenesis through its inhibition of the Tie2 signaling pathway. Upregulation leads to pathological angiogenesis, both independently and through additive effects with VEGF. Animal models have demonstrated that inhibiting Ang2 leads to decreased vascular permeability, and dual inhibition of Ang2 and VEGF leads to significant reduction in vascular permeability greater than Ang2 or VEGF alone.

Faricimab, a bispecific monoclonal antibody to Ang2 and VEGF-A, has now gone through two Phase II trials, which have demonstrated noninferiority in both q16-and q12-week injections compared with q4-week ranibizumab when evaluating BCVA and CST.

On the other hand, nesvacumab, a monoclonal antibody that inhibits Ang2, in combination with aflibercept (REGN910-3) was found to be equivalent in efficacy to aflibercept alone. Phase III trials are under way comparing faricimab in q16 week intervals to aflibercept q8 weeks. RS

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Animal models have shown that inhibiting Ang2 leads to decreased vascular permeability and dual inhibition of Ang2 and VEGF leads to significant reduction in vascular permeability greater than Ang2 or VEGF alone.

How UWF imaging can guide anti-VEGF therapy in PDR

We report on our experience using ultra-widefield imaging to evaluate endolaser-less vitrectomy in eyes with vitreous hemorrhage.

By Venkatkrish M. Kasetty, MD, Davis Starnes and Dennis M. Marcus, MD

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Take-home points

- Widefield imaging provides greater information when evaluating and managing proliferative diabetic retinopathy.
- Ultra-widefield fluorescein angiography better defines neovascularization identification, regression and progression compared to clinical examination alone.
- Despite panretinal photocoagulation or anti-VEGF therapy, eyes frequently develop vitreous hemorrhage indicating the need to further optimize PDR treatment.
- UWF-FA-guided anti-VEGF pro re nata dosing has the potential to optimize PDR outcomes and may provide a foundation for non-invasive PDR monitoring with widefield optical coherence tomography angiography.

The consequences of proliferative diabetic retinopathy, if uncontrolled, are well known: severe vision loss with vitreous hemorrhage and tractional retinal detachment.[1] While pan-retinal photocoagulation has remained the standard therapy, DRCR Retina Network Protocol S and CLARITY trial results established intravitreal injections with anti-VEGF drugs as an alternative therapy for PDR eyes that don't require vitrectomy.

Anti-VEGF agents have been shown to produce superior or equivalent visual outcomes while minimizing visual field loss and proliferative consequences compared with PRP.[2-4] While anti-VEGF agents offer many benefits, therapy is more expensive, the treatment burden is higher and follow-up and monitoring more frequent than PRP alone. Patient non-compliance with follow-up has remained an issue.[3,5]

Therefore, retina specialists often opt to administer PRP alone or in combination with anti-VEGF for PDR because PRP is thought to be more reliable in this population.[6]

Despite the favorable and equivalent five-year outcomes observed for both PRP and ranibizumab-treated eyes in DRCR Protocol S, vitreous hemorrhage occurs in almost 50 percent of eyes receiving either therapy.[3] The high incidence of proliferative complications indicates a need to evaluate how to further optimize PDR treatment.

Ultra-widefield imaging

Since 1991, diabetic retinopathy severity and progression have been graded based on the modified Airlie House classification using seven-standard field fundus (7SF) photography established in the Early Treatment Diabetic Retinopathy Study, which captures about 35 percent of the retinal area.[7-9] Imaging the peripheral retina can identify more pathology and provide further guidance in managing PDR.[10]

Ultra-widefield imaging, capturing up to 82 percent of retinal area, provides more

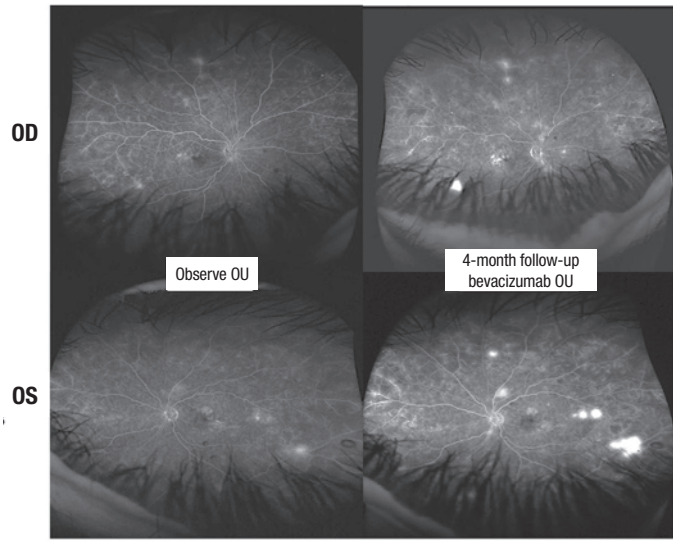

Figure 1. This patient has been receiving ultra-widefield fluorescein angiography-guided bevacizumab (Avastin, Genentech/Roche) monotherapy for proliferative diabetic retinopathy in both eyes for the past four years. To date, the patient has retained 20/20 visual acuity OU after 15 injections OD and 11 injections OS. UWF-FA on the left panel indicates stable neovascularization elsewhere (NVE) OU that was observed clinically. UWF-FA four months later demonstrated increased NVE intensity, size and leakage OU stimulating *pro re nata* dosing with bevacizumab OU.

information.[10,11] With greater adoption of widefield imaging in clinical practice, UWF imaging was recently defined as a single image centered on the fovea capturing retinal anatomy beyond the posterior pole and anterior to the vortex veins in all four quadrants.[12]

The multicenter DRCR Protocol AA study along with other single-center studies have shown agreement in assessing DR severity on EDTRS images and UWF fundus photography.[13-16]

Retinopathy peripheral to the EDTRS fields is identified in up to 40 percent of eyes on UWF imaging, resulting in increased DR severity in 9 to 15 percent of eyes. Eyes with peripheral retinopathy have also been shown to have higher rates of DR progression compared to eyes without peripheral retinopathy.[10,11,13-23]

For years, the American Academy of Ophthalmology preferred practice patterns didn't recommend FA as a necessity in the diagnosis and management of PDR. With the incorporation of widefield FA as a supplement to fundus photography and clinical examination, it has emerged as a valuable tool.[8,24]

UWF-FA obtains images with 3.2 times more retinal area than the 7SF images, revealing nonperfusion, ischemia, vascular leakage and neovascularization not evident with fundus photography or clinical examination. These lesions have clinically significant implications on PDR management.[6,11,22,23,25-27] Area of retinal nonperfusion, often imaged in the mid-peripheral retina, is predictive of developing or finding PDR and neovascularization.[28]

UWF-FA Guided Anti-VEGF Therapy

PDR eyes treated with anti-VEGF agents have shown retinal neovascularization regression and reperfusion on both widefield and standard-field FA.[29-33] Our clinical experience indicates that UWF-FA identifies neovascularization regression and progression better than clinical examination alone. So, when electing anti-VEGF monotherapy for PDR, we've found using UWF-FA beneficial (*Figure 1*). Our experience in the care of PDR eyes led us to include this approach within our clinical trial (LASERLESS Trial) evaluating endolaserless (omitting PRP endolaser) vitrectomy for PDR eyes with vitreous hemorrhage. We utilized UWF-FA-guided aflibercept (Eylea, Regeneron Pharmaceuticals) PRN dosing (in addition to mandatory postoperative aflibercept) in PDR eyes after endolaserless vitrectomy.

We previously reported results for 31 LASERLESS trial eyes.[34-37] Four-month results demonstrated quick visual acuity

Bios

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Disclosures: Dr. Kasetty and Mr. Starnes have no financial relationships to disclose.

Dr. Marcus disclosed relationships with Regeneron Pharmaceuticals, Genentech/Roche, Allergan (AbbVie), Alcon, Aerpio Pharmaceuticals, Kalvista Pharmaceuticals, Ionis Pharmaceuticals, Mylan, Samsung Bioepis, Novartis, Opthea, Chenghdu, Clearside Biomedical, Astellas Pharma, Allegro Ophthalmics, Alimera Sciences, Iveric bio, Outlook Therapeutics, Gemini Therapeutics, ThromboGenics, Tyrogenex, Graybug Vision, Topcon, Optos, Xplore, Gyroscope Therapeutics, Stealth BioTherapeutics, Spiam, Aerie Pharmaceuticals, Apellis Pharmaceuticals, OHR Pharmaceutical, Regenxbio, Kodiak Sciences and Zeiss.

(VA) gains with an improvement of 38 to 72 (20/40) letters.[35] One-year results indicated safety, moderate-term durability and significant VA improvement.[36]

Additionally, neovascularization was absent on UWF-FA in 70 percent and 27 percent of q8- and q16-week eyes, respectively. Our two-year results indicate that persistent and frequent postoperative anti-VEGF therapy is necessary to optimize visual outcomes and reduce complications.[37]

We also evaluated using UWF-FA to guide *pro re nata* aflibercept monotherapy in 17 PRP-naïve PDR eyes not requiring vitrectomy (*Figures 2 and 3*). Through one year, we observed excellent safety and a 4-letter VA gain. We also observed an absence of neovascularization on UWF-FA in 41 percent of eyes at four weeks after the first aflibercept injection. Progression after regression of neovascularization occurred as only 24 percent of eyes demonstrated absence of neovascularization at one year despite an average of 5.7 injections administered.[38]

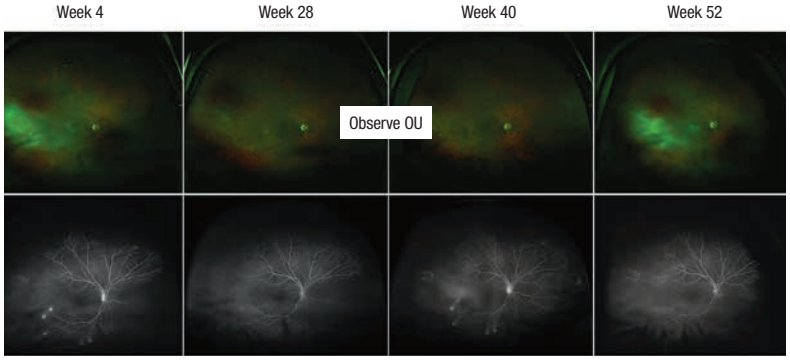

Figure 2. Ultra-widefield fundus angiography and UWF fundus photography of a 74-year-old Black female on aflibercept (Eylea, Regeneron Pharmaceuticals) monotherapy for proliferative diabetic retinopathy OD not requiring vitrectomy. She was treated with aflibercept at weeks four, eight, 12 and 40. At baseline, neovascularization was present, but progressively improved until it resolved at week 28. Neovascularization recurred at week 40. Best-corrected visual acuity at any point over 52 weeks was 20/80, improved from 20/125 at baseline.

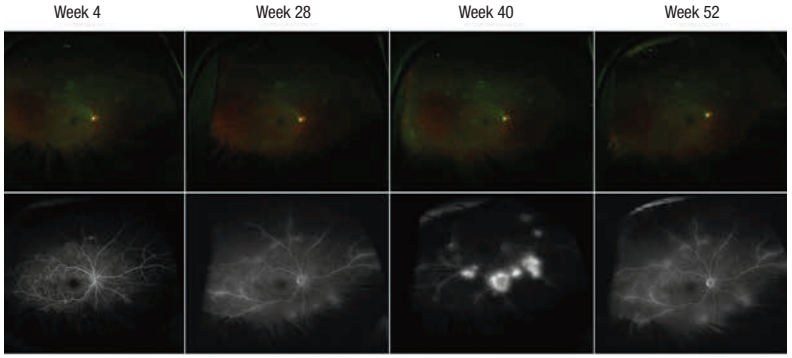

Figure 3. Ultra-widefield fundus angiography and UWF fundus photography of a 41-year-old White male receiving aflibercept (Eylea, Regeneron Pharmaceuticals) monotherapy for proliferative diabetic retinopathy OD not requiring vitrectomy. He was treated with aflibercept at baseline and weeks four, eight, 12, 16, 24, 32, 40, 44 and 48. Neovascularization improved until week 40 when progression was observed. Best-corrected visual acuity at any point over 52 weeks was 20/20, improved from 20/25 at baseline.

Is PRP more durable?

While PRP is commonly believed to be more durable in treating PDR than anti-VEGF agents, it hasn't been definitively confirmed in major PDR trials. In the CLARITY study, 65 and 6 percent of eyes required additional PRP and vitrectomy, respectively, through one year.[4] In the PROTEUS study, 44 percent of eyes receiving PRP and ranibizumab showed complete neovascularization regression compared to 25 percent of eyes receiving PRP alone.[39]

In many large PDR trials, neovascularization status was monitored by clinical examination alone, which may have resulted in missed neovascularization progression. Without the use of widefield FA, we may be undertreating PDR, resulting in significant vitreous hemorrhage rates. Thus, UWF-FA guided anti-VEGF PRN dosing has the potential to reduce proliferative complications and vitreous hemorrhage rates in PDR eyes even after PRP.

Widefield OCTA

Optical coherence tomography angiography, a newer imaging method that allows for three-dimensional visualization of the retinal microvasculature, has been reported to successfully depict DR lesions, even revealing vascular abnormalities in people with diabetes with a normal fundus on ophthalmoscopy.[24] It offers advantages over FA, including the ability to view neovascularization and determine its location as preretinal

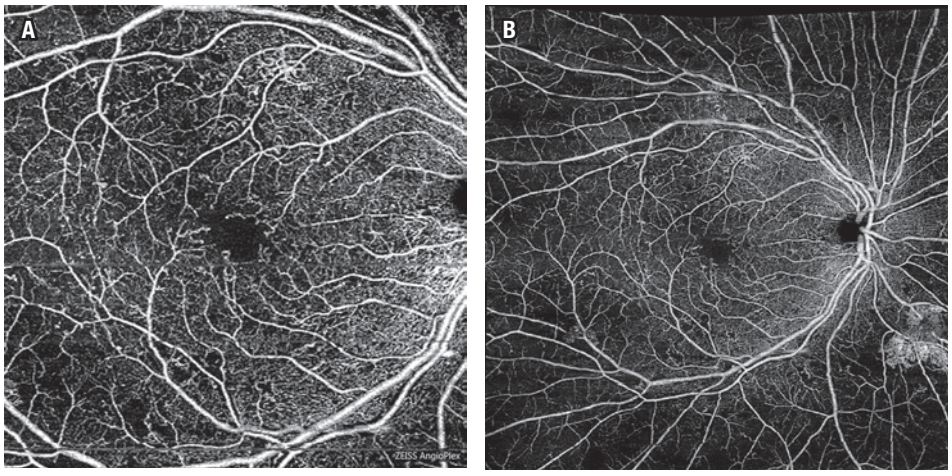

Figure 4. An 8-x-8-mm optical coherence tomography angiograph (A) compared to 14-x-14-mm widefield OCTA (B) for detection of proliferative diabetic retinopathy. (*Courtesy Zeiss*).

or intraretinal.[40]

OCTA can also detect diabetic macular ischemia as well as FA.[41,42] Recent studies have demonstrated that widefield OCTA may be an appropriate imaging modality for managing PDR, providing information about neovascularization comparable to UWF-FA.[43] Figure 4 compares widefield OCTA with standard field OCTA.

Widefield OCTA has been proposed to be the only imaging modality required to monitor neovascularization status in PDR after PRP.[40] It's important to note, however, that while FA can show decreased neovascularization leakage after PRP or anti-VEGF, OCTA can't detect this, thus potentially limiting its ability to assess neovascularization progression or regression.[44] However, as OCTA detects nonperfusion better than FA, the need to further evaluate its role in PDR management exists.[26,45]

Future study focus

Even though UWF-FA is frequently used in clinical practice, limited data exists evaluating UWF-FA-guided PRN anti-VEGF dosing. However, as UWF imaging has been shown to detect peripheral retinopathy and neovascularization not easily observed on clinical exam and fundus photography, we believe that wide-field angiographic monitoring is a useful tool to monitor proliferative activity and optimize anti-VEGF therapy needs, thus reducing proliferative consequences.

Using UWF imaging in PDR eyes is especially important because neovascularization assessment on fundus exam can be confounded by a lack of patient cooperation, phakic status, and profound retinal ischemia and flat neovascularization that are difficult to assess on exam. While our widefield FA monitoring approach is limited by absence of control groups, it's analogous to early nAMD trials (PrONTO), which based anti-VEGF treatment on anatomical changes observed on OCT.[46]

Bottom line

UWF-FA guided anti-VEGF PRN dosing has the potential to optimize PDR outcomes and may provide a foundation for non-invasive PDR monitoring with widefield OCTA, especially as continued use and advancements in wide-angle and widefield montage OCTA emerge.[24,26,40-45]

We also hope that our widefield FA-guided findings stimulate further evaluation on monitoring PDR activity with UWF-FA and of various dosing regimens for PDR. DRCR Retina Network Protocol AA results will provide additional important information on widefield imaging in DR. RS

(References continued on page 32)

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UWF-FA guided anti-VEGF PRN dosing has the potential to optimize PDR outcomes and may provide a foundation for non-invasive PDR monitoring with widefield OCTA.

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Retina Standouts from ASRS 2020

Novel approaches to PVR, RP and macular hole surgery

Here are five noteworthy presentations from the virtual gathering of global retina specialists.

By Ashkan M. Abbey, MD

Take-home points

- A treat-and-extend approach with intravitreal methotrexate shows promise as a less-burdensome option for proliferative vitreoretinopathy.
- Optogenetics for nonsyndromic retinitis pigmentosa may have the potential to treat other retinal diseases causing photoreceptor loss.
- A technique of creating multilayered inverted internal limiting membrane flaps showed a high degree of success in closing large macular holes.
- Subretinal transplantation of an amniotic membrane helped promote closure of persistent full-thickness macular holes.
- A relatively simple relaxing parafoveal nasal retinotomy after ILM peeling achieved closure of 13 of 15 large or refractory macular holes.

For the first time in its history, the annual meeting of the American Society of Retina Specialists occurred virtually due to the ongoing COVID-19 pandemic. Leading retina specialists from around the world came together online to demonstrate how rapidly the field of retina is advancing.

Here, we present five intriguing presentations: management of proliferative vitreoretinopathy (PVR) using intravitreal methotrexate; optogenetics for retinitis pigmentosa; and three novel techniques to close persistent and/or large macular holes.

PVR management using treat-and-extend methotrexate

PVR continues to be every retina surgeon's worst nightmare. Previous studies in animal models and humans have shown efficacy of PVR prevention with the use of intravitreal methotrexate. Scott D. Walter, MD, MSc, presented a study that looked at a more manageable treat-and-extend protocol for the use of intravitreal methotrexate (400 µg/0.1 mL) in these patients.[1]

Initial loading doses were administered every one to two weeks after surgery until the lasered edge of the retinectomy had matured and stabilized. Then the treatment interval was extended into the three- to six-week range until silicone oil removal.

Previous protocol recommendations included approximately 12 injections before silicone oil removal, but most patients in this study received six or fewer injections, with a median of three during the loading phase and a median of two during the extension phase. An additional injection was given at the time of silicone oil removal.

The updated series included 50 eyes of 50 patients with severe grade B or grade

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Bio

Dr. Abbey is a surgical and medical retina specialist at Texas Retina Associates, Dallas, and clinical assistant professor of ophthalmology at the University of Texas Southwestern Medical Center.

DISCLOSURES: Dr. Abbey is a consultant to Allergan/AbbVie and Genentech/Roche.

C PVR. The final reattachment rate was 96 percent, and the single-operation success rate 88 percent; 78 percent achieved ambulatory vision at last follow-up. Notably, nearly 40 percent developed keratopathy.

PVR remains one of the greatest challenges in vitreoretinal surgery. Intravitreal methotrexate appears to be effective at mitigating the risk of PVR formation. Previous protocols, however, were quite burdensome. This study suggests that similar outcomes may be achieved with a less onerous treat-and-extend injection protocol. That may convince more surgeons to adopt this treatment for high-risk patients.

Dr. Walter, of Hartford Hospital and the University of Connecticut School of Medicine, disclosed financial relationships with Allergan/AbbVie, Castle Biosciences and Genentech/Roche.

Optogenetics as an option for nonsyndromic RP

More than 100 different genetic mutations can cause RP. Targeting each mutation with gene therapy would be a costly and extremely difficult task for our scientific community. Optogenetics is a technique in which genetic modification of a neuron encodes a light-sensitive opsin protein, allowing neuronal cells to respond to light stimulation. In the retina, this therapy involves genetic modification of ganglion cells with a channel rhodopsin that makes retinal ganglion cells photosensitive.

Optogenetic gene therapy is an exciting new approach to treatment for inherited retinal diseases that could also be applied to other retinal diseases causing photoreceptor loss.

In retinal diseases like RP that result in photoreceptor loss, conferring photosensitivity in retinal ganglion cells may potentially restore vision. Optogenetic gene therapy is "gene agnostic," meaning that it could theoretically be utilized for any of the mutations causing RP.

PIONEER is a first in-human dose-escalation trial of patients with end-stage nonsyndromic RP (light perception or worse vision) regardless of the underlying genetic defect.[2] The treatment combines the simultaneous action of a gene therapy with a light-stimulating medical device.

A single intravitreal injection delivers viral vectors carrying the gene encoding ChrimsonR, a light-sensitive opsin derived from green algae. It targets the retinal ganglion cells to make them photosensitive upon gene transfer. After the injection, the patient wears photostimulating goggles with an event-based camera and a projection amplifying light source. These goggles amplify light onto the retina to overcome the low light sensitivity of the ChrimsonR channel rhodopsin. Low-vision and vision training sessions after treatment teach the patient how to use the device.

Joseph Martel, MD, reported no serious adverse events in seven patients in the trial. All patients tolerated the light-stimulating goggles well. The most common ocular adverse event was mild intraocular inflammation, which responded to topical corticosteroids.

Optogenetic gene therapy is an exciting new approach to treatment for inherited retinal diseases that could also be applied to other retinal diseases causing photoreceptor loss. Long-term visual outcomes for the patients in the PIONEER trial will be highly anticipated by the retina community.

Dr. Martel of the University of Pittsburgh has no relevant financial disclosures.

Novel surgical techniques for large or persistent macular holes

In recent years, several novel techniques for closing large and/or persistent full-thickness macular holes have emerged with varying degrees of success. Complications include inverted internal limiting membrane flaps, lens capsular flap transplantation and macular hole hydrodissection. Each technique has advantages and disadvantages, and surgeon preference can vary. These three presentations described positive outcomes of novel techniques.

Multilayered inverted ILM flap

This technique is useful in eyes with large macular holes (>700 µm) without a previous ILM peel. It involves a vitrecto-

my followed by creation of a multilayered inverted ILM flap. Srinavas Joshi, MD, reported on the technique of creating multiple ILM flaps in a "petaloid" fashion using ILM forceps and starting 1 to 2 disc diameters from the macular hole.[3]

The ILM "petals" were placed one over the other in the macular hole under perfluorocarbon liquid (PFCL). Intraoperative OCT confirmed the position of the stacked ILM flaps. All cases used C3F8 gas and required one week of postoperative prone positioning.

Dr. Joshi reviewed 103 eyes of 99 patients. Mean minimum macular hole diameter was 711.96 µm, and mean basal diameter 1,390.14 µm. At three months postop, 92.2 percent achieved type 1 closure, 5.8 percent type 2 closure and 1.9 percent type 3 closure. Mean preoperative best-corrected visual acuity was around 20/320 and improved to 20/125 at three months.

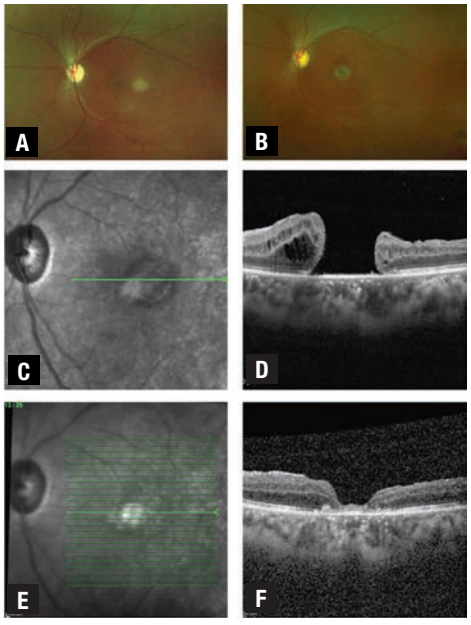
A conventional inverted ILM flap carries a risk of dislodging from the hole during fluid-air exchange (FAX). The rate of spontaneous detachment of the flap was 14 percent in the original published case series. With the multilayered technique, even if one flap petal becomes dislodged, multiple additional ILM flaps remain to promote closure. In this series, none of the 103 eyes had flap dislodgement during FAX.

One distinct disadvantage of this technique is the high cost of using PFCL for the ILM peel. Furthermore, peeling ILM under PFCL can be technically challenging.

Dr. Joshi of the M.M. Joshi Eye Institute, Hubli, India, has no relevant disclosures.

Amniotic membrane transplant

This technique uses forceps to insert a folded, circularly-punched patch of amniotic membrane through a valved trocar and into the macular hole (*Figure*). Jessica Lee, MD, described the outcomes of amniotic membrane transplantation in eight patients with persistently open large macular holes after vitrectomy with ILM peeling.[4] Six patients had tamponade with gas and two with silicone oil. All holes were closed at the one-week postop visit. Mean BCVA improved from 20/1,000 to 20/320 at three months for five holes.



Pre- and postoperative images of full-thickness macular holes that have undergone amniotic membrane transplantation: (A) fundus photograph preoperatively and (B) two-months after the procedure; (C) preoperative *en face* optical coherence tomography and (D) preoperative OCT depicting full thickness macular hole; and (E) *en face* OCT two months postoperatively and (F) OCT two months postoperatively. (*Courtesy Jessica Lee, MD*)

One advantage of this technique is that it eliminates the need to harvest an ILM flap outside the macula center, which can be tedious and difficult in eyes with previous large-diameter ILM peels. It also provides a safer substrate to "bridge" large holes than autologous retinal transplantation, which has a higher risk of retinal detachment.

Disadvantages include the additional cost of using an amniotic membrane and the degree of difficulty associated with preparation and appropriate insertion of the amniotic membrane into the hole.

Dr. Lee of New York Eye and Ear has no relevant financial disclosures.

Paracentral retinotomy

This relatively simple yet effective technique involves a relaxing parafoveal nasal retinotomy after ILM peeling in large or refractory macular holes. Theoretically, this further reduces tangential traction around the hole to facilitate closure. After ILM peeling, endodiathermy is applied to create

(Continued on page 38)

Untangling the web of 'bundles'

The National Correct Coding Initiative prohibits selected coding bundles, so if you must bundle, just submit one code—the higher one.

By Ellen R. Adams, MBA

Have a question for "Coding Commentary"? Tweet it to us at **@RetSpecMag**

Bio

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COVID-19 has tangled our world into a web of disruption at every turn. For many clinics, testing has been deferred to minimize patient-clinician contact and patient time in the clinic. But now it's important to get back up to speed on testing rules to avoid costly errors. Denied claims are especially painful as we try to recover from the toll of COVID-19.

'Bundled' services

You may recall from previous articles that Medicare has a program called the National Correct Coding Initiative (NCCI). NCCI rules create "bundles" of services that aren't permitted to be billed together when performed on the same date of service. Even when we were running our practices in what was our prior state, bundles caused confusion for our most commonly performed retina testing: optical coherence tomography, fundus photography and extended ophthalmoscopy.

OCT of the retina (92134) has been mutually exclusive with fundus photography (92250) since 2011, when CPT 92134 was implemented. It's important to note that FA (92235) and ICG angiography (92240) are *not* bundled with OCT. Interestingly, OCT isn't bundled with extended ophthalmoscopy (92201 and 92202), although many payer policies discourage the combination.

Although extended ophthalmoscopy (92201 or 92202) isn't bundled with OCT, it is bundled with fundus photography. You may encounter circumstances where a photograph of a glaucomatous optic nerve (92250) is appropriate on the same date of service as an extended ophthalmoscopy of a peripheral nevus (92201).

Because 92250 and 92201 are bundled, if you submit a claim for both services you will most likely be reimbursed for the lower-paying code (92201). A more logical strategy is to submit the claim for only the higher-paying photography code and not bill the extended ophthalmoscopy. Alternatively, if either test is nonurgent, you could consider performing them on separate days. It wouldn't be wise to attempt to "break the bundle" on the NCCI edit just to get paid.

Untangling the bundles

One significant consideration is submitting a claim for the higher-paying test when you perform bundled services that have the same level of medical necessity on the same date. This is critical.

Assuming all testing carries the same weight of medical necessity, the accompanying table will help you untangle the bundles by reimbursement levels. Note that when billing more than two tests, Medicare's multiple procedure payment rules will change the reimbursement for some tests with a lesser-valued technical component.

Recovery mode

We hope you're able to recover from the pandemic and use the crisis as a learning experience to improve clinical procedures. It may be that your need to move patients through the clinic more efficiently leads to a strain on your ability to document, select appropriate codes and in general pay attention to the minutiae of billing. We hope this will get your thought processes re-engaged, allowing you to optimize your revenue during recovery.

Stay safe.

Codes for a CPT bundle

CPT Bundle	RVU	Submit claim for
92250, 92134	1.27, 1.15	92250
92250, 92202	1.27, 0.43	92250
92250, 92235	1.27, 2.93	Both
92250, 92240	1.27, 4.35	92240
92134, 92202	1.15, 0.43	92134
92235, 92250, 92134	2.93, 1.27, 1.15	92235, 92250
92250, 92134, 92202	1.27, 1.15, 0.43	92250

Source: Medicare Physician Fee Schedule 2020

Department Editor **Emmett T. Cunningham Jr., MD, PhD**

PDS with ranibizumab: It's in the technique

A closer look at Archway results and 'a few important details' for the implantation procedure that drives outcomes.

By Richard Mark Kirkner, Editor

The Port Delivery System with ranibizumab (PDS) has been the focus of much attention in the late summer. Phase III Archway trial data presented at the American Society of Retina Specialists showed the vast majority of patients—98.4 percent to be precise—went six months before needing any additional treatment.[1]

Some basics about PDS with ranibizumab: It's a refillable eye implant that Genentech/Roche describes as the size of about a grain of rice. The manufacturer also emphasizes that the ranibizumab in the PDS is different from Lucentis used for intravitreal injection. The PDS is designed to continuously deliver a formulation of ranibizumab into the eye over a course of months and eliminate the need for more frequent intravitreal injections.

The Archway trial consists of 418 participants with neovascular age-related macular degeneration randomized to PDS with 100 mg/mL ranibizumab or intravitreal injections of 10 mg/mL Lucentis. The primary outcome measure was the mean change from baseline best-corrected visual acuity averaged over weeks 36 and 40. Data collection ended in March, with the study completion expected mid-spring next year.

Here, principal investigator Peter A. Campochiaro, MD, of the Wilmer Eye Institute at Johns Hopkins University in Baltimore, and who presented the Archway results at ASRS, answers questions about the trial and the PDS with ranibizumab itself.

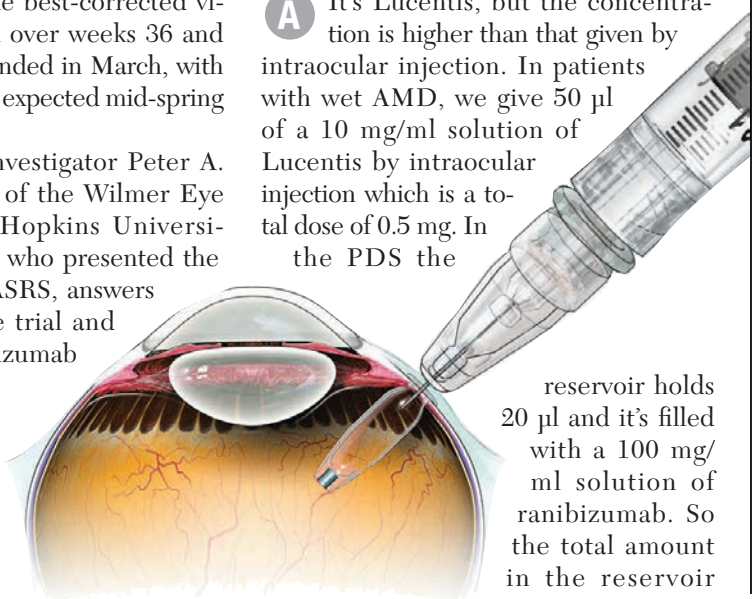
Q Everyone understands the mechanism of ranibizumab well. Does the sustained release via PDS alter the bioavailablity of the drug in any way?

A Yes, it makes the drug available continuously unlike intraocular injections which result in peaks and valleys. Depending on the frequency of intraocular injections, there are periods when there is no ranibizumab in the eye, whereas with the PDS ranibizumab is present in the eye continuously.

After implantation of the PDS or refill/exchange, the level of ranibizumab in the eye is greater than trough levels seen with monthly injections for 12 months. The amount of ranibizumab needed for efficacy varies somewhat among patients, but at six months after implantation the levels of ranibizumab in the eye are in the therapeutic range for almost all patients. That's why refill/exchanges are done every six months.

Q How does this formulation differ from Lucentis?

A It's Lucentis, but the concentration is higher than that given by intraocular injection. In patients with wet AMD, we give 50 µl of a 10 mg/ml solution of Lucentis by intraocular injection which is a total dose of 0.5 mg. In the PDS the reservoir holds 20 µl and it's filled with a 100 mg/ml solution of ranibizumab. So the total amount in the reservoir



A rendering of refilling the Port Delivery System with ranibizumab. (*Courtesy Genentech/Roche*)

After implantation of the PDS or refill/exchange, the level of ranibizumab in the eye is greater than trough levels seen with monthly injections for 12 months.

is 2 mg but it's released slowly into the eye.

Q What's involved with the implantation process?

A It's a very easy procedure, but it's important to pay attention to a few important details.

It's usually done under local anesthesia with sedation. A 27-gauge cannula is inserted and an infusion line is attached but not turned on. A conjunctival flap is dissected in the superotemporal quadrant taking care to dissect under Tenon's capsule so that it remains attached to the conjunctiva. A radial incision is made in the horizontal meridian. Light cautery is applied to the episclera to obtain hemostasis, and then at 4 mm posterior to the limbus a 3.5-mm incision is made through the sclera to expose the pars plana.

The pars plana is treated with long-duration, overlapping burns of laser photocoagulation to cauterize all the blood vessels within it. One should check to make sure the infusion is off and then an MVR blade is used to penetrate the pars plana. The PDS is then inserted with a PDS-insertion tool and it's tamped down to make sure the flange and septum protrude as little as possible above the scleral surface.

The conjunctiva, with Tenon's capsule attached, is then closed, making sure to place two episcleral bites to secure it at the limbus. The limbal edge of the conjunctiva should actually overlap the peripheral edge of the cornea so that as it retracts, it settles down right at the limbus.

Q What's the most significant finding of the Archway trial?

A The most significant finding is that, compared with monthly injections of ranibizumab, the PDS showed equivalent maintenance of visual acuity.

Q What was the most surprising finding from the trial?

A That 98 percent of patients in the PDS group didn't require a supplemental injection prior to the first refill/exchange. This indicates excellent reliability in reaching the target duration. With any sustained delivery approach, high reliability is important to eliminate the need for extra visits for monitoring.

Q Are there any secondary findings of significance?

A In a patient-reported outcome survey, patients reported a strong preference for the PDS over intraocular injections.

Q Were there any safety issues with the implantation and refill procedures?

A There were four cases of endophthalmitis, three of which were related to conjunctival retraction, so appropriate management of the conjunctiva is important as emphasized earlier. One of these patients had permanent, severe vision loss, but the other three were effectively treated and vision returned to baseline.

Q What's the next readout we can expect from the trial?

A Long-term outcomes will be reported after all patients complete the week 96-visit.

REFERENCE

1. Campochiaro P. Primary analysis results of the Phase 3 Archway trial of the port delivery system with ranibizumab (PDS) for patients with neovascular AMD. Paper presented at American Society of Retina Specialists 2020 virtual annual meeting; July 26, 2020.

Novel approaches to PVR, RP, macular hole surgery

(Continued from page 35)

a small retinotomy at the midpoint between the fovea and optic disc. Slow suction then at the retinotomy site uses a soft-tip cannula. Additional suction at the retinotomy occurs during FAX. The hole diameter narrows as the suction brings the edges together. Either SF6 or C3F8 gas is used. Seven to 10 days of prone positioning is recommended.

Michael S. Tsipursky, MD, reported on a series of 15 eyes.[5] Mean basal diameter of the holes was 1,300 µm, and 13 of 15 eyes had refractory macular holes following one or more vitrectomies with ILM peeling.

Macular hole closure was achieved in 13 of 15 eyes (86.7 percent); 11 of 15 (73.3 percent) achieved BCVA improvement during postop follow-up. Mean BCVA improved from 20/400 at baseline to 20/160 at last follow-up.

This is a simple and inexpensive way to close large or refractory macular holes. One disadvantage is that the retinotomy may create a paracentral scotoma, but the authors believe that for most patients the functional vision gains outweigh that risk.

Dr. Tsipursky of the University of Illinois, Urbana, has no relevant financial disclosures.

REFERENCES

1. Walter S. Management of proliferative vitreoretinopathy with intravitreal methotrexate using a treat-and-extend protocol. Paper presented at American Society of Retina Specialists 2020 Virtual annual meeting; July 25, 2020.
2. Martel JN, Esposti S, Boulanger-Scemama E, et al. Optogenetics in the clinic: PIONEER, a Phase I/II gene therapy program for non-syndromic retinitis pigmentosa. Poster presented at ASRS 2020 Virtual annual meeting; July 25, 2020.
3. Joshi S, Yadav N, Ayachit AF, Ayachit GS. Multilayered inverted internal limiting membrane flap—a unique technique for closure of large macular holes. Paper presented at ASRS 2020 Virtual annual meeting; July 25, 2020.
4. Lee J, Chua M, Jansen JE, et al. Amniotic membrane subretinal transplantation to promote closure of persistent full-thickness macular holes. Paper presented at ASRS 2020 Virtual annual meeting; July 24, 2020.
5. Tsipursky MS, Byun MJ, Sheth VS, Jager RD. Update on paracentral retinotomy for resistant macular hole. Paper presented at ASRS 2020 Virtual annual meeting; July 25, 2020.

YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

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

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

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

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

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

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

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

(continued)

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

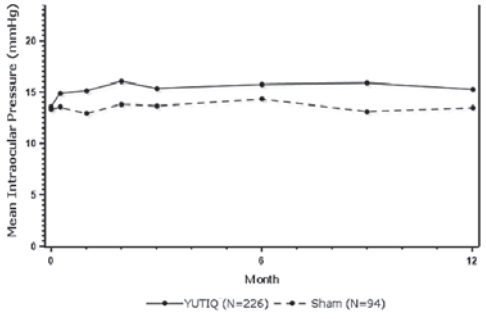
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

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

Table 2: Summary of Elevated IOP Related Adverse Reactions

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

Figure 1: Mean IOP During the Studies



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

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

Discover continuous calm in uveitis

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg:

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

J code: J7314

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

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

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

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Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

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

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

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

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