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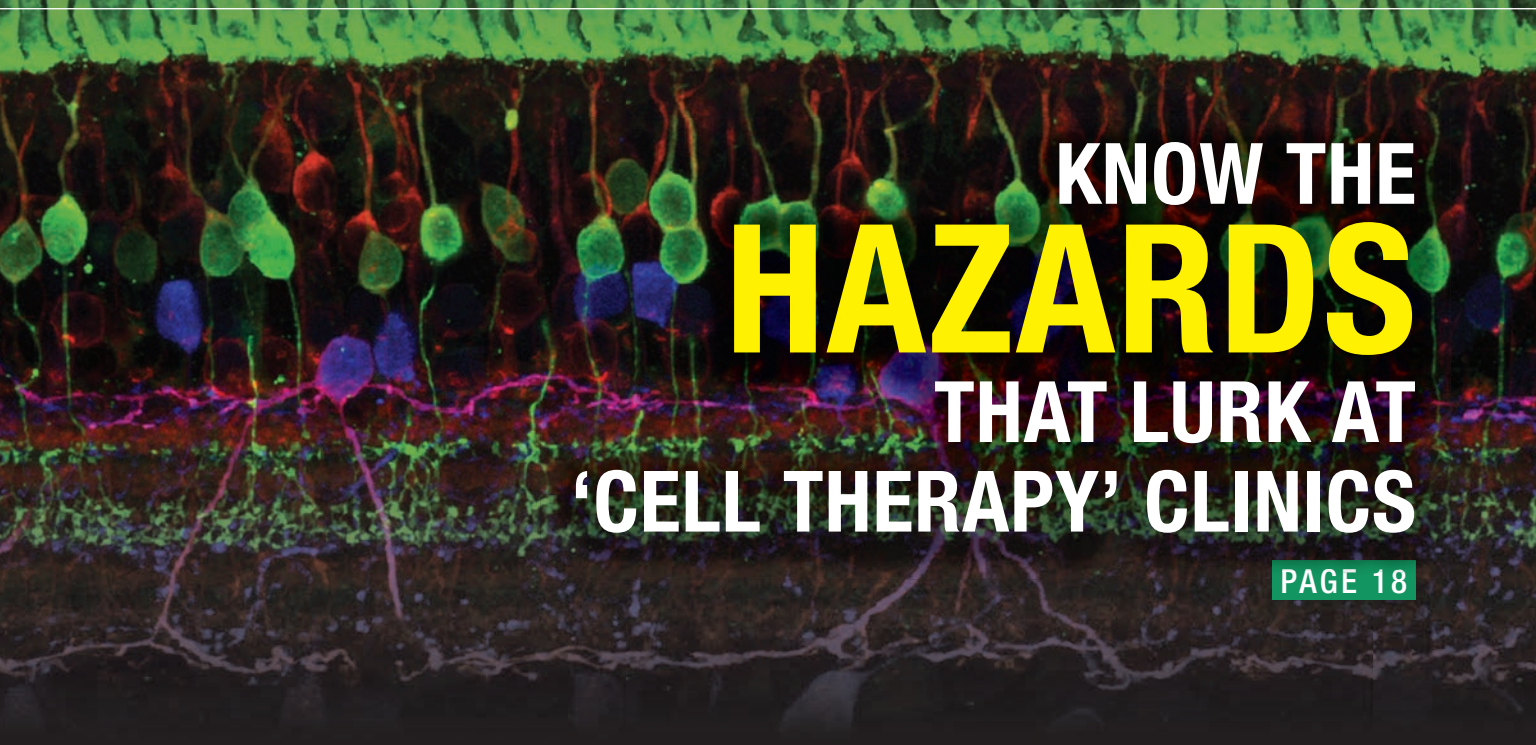

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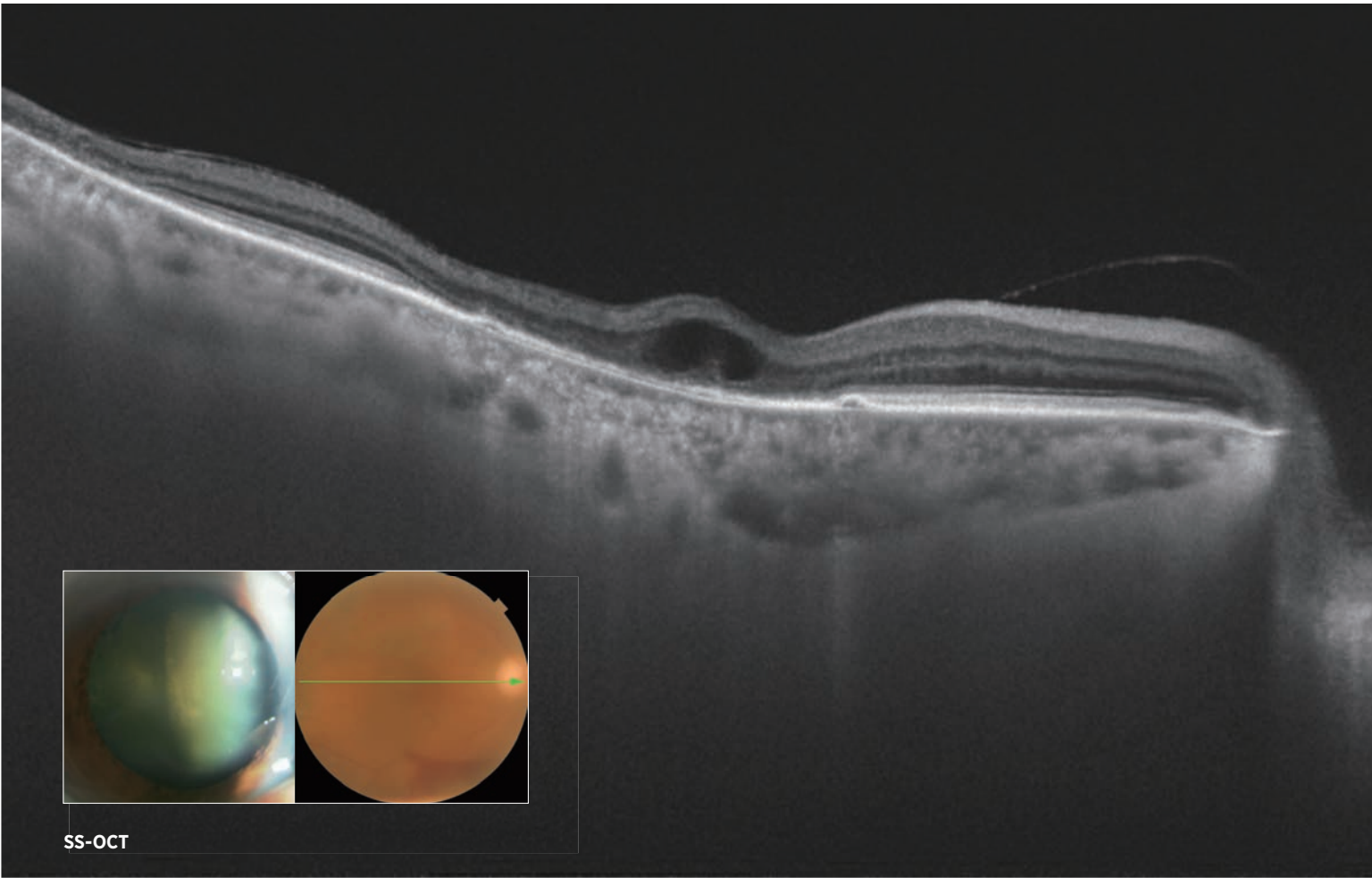

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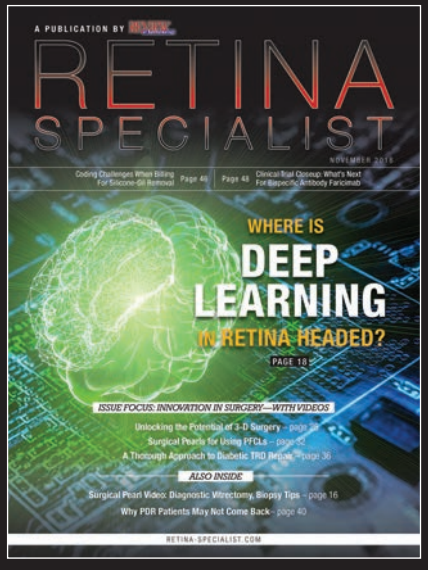

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EDITORIAL

By Charles C. Wykoff, MD, PhD

The devastation of diabetic retinopathy

I grew up in California's Central Valley, about a hundred miles south of the recent Camp Fire that claimed the lives of at least 85 people. Stories of heroism mixed with frustration and a failed evacuation have been on my mind. While images of pain and devastation are a mainstay of our news feeds, those from Butte County were particularly disturbing to me. The whole area seems to have been charred to a crisp.

An eye lost to tractional retinal detachment or neovascular glaucoma secondary to unrestrained diabetic retinopathy reminds me of such loss.

The tragedy in both situations, loss of life in California and permanent loss of vision in diabetic retinopathy, is that both could have likely been avoided. Many cases of end-stage diabetic retinopathy can be attributed to at least one of two system failures:

- ***Failure of detection.*** In the United States, about half of diabetic patients do not receive their recommended retinopathy screening. Some societies, including those of the United Kingdom, Denmark, Sweden and Iceland, appear to have largely solved this problem. For example, thanks to a systematic screening approach used across the United Kingdom, diabetes has fallen from the first to the fourth most common cause of visual impairment over the past decade. Bravo!
- ***Failure of adherence to treatment recommendations.*** Unfortunately, the terminology we use to describe this clinical situation, "non-compliance" and "loss to follow-up," carry negative connotations, implying that lack of adherence to a given follow-up recommendation is an intentional patient choice. In many cases this is likely not the case, as a multitude of obstacles, many outside of the patient's immediate sphere of influence, can impact a patient's ability to return to a given physician appointment.

See page 27 where Daniel Su, MD, and colleagues describe the Wills Eye Hospital experiences with compliance among proliferative DR patients and clinical outcomes after being lost to follow-up for six months or more.

We as retina specialists need to encourage our patients in their medical and personal struggles to maintain compliance, be innovative in developing and implementing better approaches to achieve universal screening, and champion the best treatments for our patients to ensure optimal long-term outcomes. Currently we lose too many eyes to the devastation of diabetic retinopathy.

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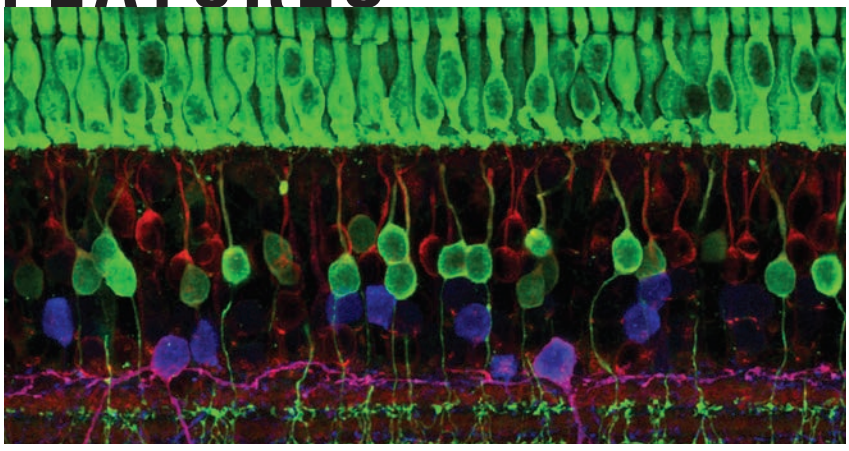
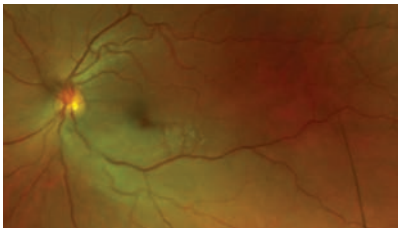
JANUARY/FEBRUARY 2019 • VOL. 5, NO. 1

FEATURES



DEPARTMENTS



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Can CMS fix step-therapy rollout in a year?

Ophthalmologists, retina subspecialists and a host of other medical disciplines are hoping that Medicare hits the reset button next year on step-therapy rules for Medicare Advantage plans. This year's plunge into "fail first," which circumvented the normal rule-making process, has rankled a broad spectrum of medical specialty societies and may even have caught the insurance companies that administer the Medicare managed-care plans off guard.

The Academy of Ophthalmology, American Society of Retina Specialists and American Glaucoma Society joined with the American Medical Association, along with 45 other medical specialty organizations and all 50 state medical societies, in sending a strongly worded letter imploring Center for Medicare and Medicaid Services administrator Seema Verma to walk back her plan that allowed Medicare Advantage plans to cover step therapy for physician-administered Part B drugs beginning January 1. The American Society of Cataract and Refractive Surgery sent its own letter in January. The program went into effect anyway.

Quotable

"This memo from August just came out of the blue and it didn't get adequate discussion from medical organizations about what's wrong with that approach."

— John Thompson, MD

It was the second time in months that the AAO, ASRS and other groups petitioned CMS to rethink a new policy. Previously, the ophthalmology societies joined with 170 other medical groups criticizing proposed rules to collapse payment rates for office visit services.

This latest round started in August when Ms. Verma came out with an edict of sorts to launch the step therapy initiative by January 1. The idea is to give MA plans a vehicle to make less-expensive therapies available as first-line treatments and then "step up" to more expensive therapies when patients fail to respond—that is, off-label Avastin before Lucentis or Eylea.

The normal rule-making process involves federal agencies publishing proposed rules, opening a comment period to receive input from stakeholders, and then drafting final rules before implementing them. But Ms. Verma short-circuited that process with her memo that rescinded a 2012 CMS memo that imposed a prohibition on step therapy for Part B. In late November 2018 CMS did publish proposed rules and opened a comment period (that since closed in late January)—but that was for rules to go into effect in 2020, not this year. MA plans already have the green light to allow step therapy thanks to Ms. Verma's vague guidance.

"This memo from August just came out of the blue and it didn't get adequate discussion from medical organizations about what's wrong with that approach," says John Thompson, MD, former

2019 brings new look, new columnists, new print schedule to *Retina Specialist*

This first issue of the year of *Retina Specialist* is reaching you earlier this year than the first issue did last year. That's because in 2019 *Retina Specialist* is increasing the frequency of its print and website publication to six times in 2019 from four times in the first four years of publication.

We've made a few other changes within our pages, too. Features and columns have been redesigned to make them easier to read and highlight take-home points.

We've added a number of new columnists, some of whom will appear in every issue, others who will rotate every other issue. This issue includes "Imaging Forum," in which Jason Hsu, MD, of Wills Eye Hospital and Mid Atlantic Retina will share compelling cases in which imaging plays a key role in diagnosis and management.

Also, David R.P. Almeida, MD, MBA, PhD, will provide practice-building ideas for using social media in "Social Media Specialist," which will appear in every issue.

Starting with the March/April issue, a new column on the management of ocular oncology will appear with Tara A. McCannel, MD, PhD, as editor. Dr. McCannel is director of the Ophthalmic Oncology Center at UCLA Stein Eye Institute. Also, Kari Rasmussen, chief operating officer of Rocky Mountain Retina Consultants of Salt Lake City, resurrects the "Retina CEO" column in which her administrator colleagues share business management strategies. And in the May/June issue, we'll introduce a new department focusing on uveitis cases with Ashkay Thomas, MD, MS, as editor. Dr. Thomas is an associate in vitreoretinal surgery and uveitis at Tennessee Retina.

Can CMS fix step therapy rollout in a year?

ASRS president and now chair of its council on health policy.

MA plans seem to be embracing the idea, even if they only had months to get ready for it. Michael Anderson, chief pharmacy officer for UnitedHealthcare's Medicare business, said in a press release, "Expanding the use of step therapy is a positive step forward." Some health-policy analysts say it could encourage drug makers to be more aggressive in negotiating discounts with pharmacy benefit managers in order to get their drugs on the first step.

Ms. Verma's guidance calls for MA plans to share savings from step edits with patients in the form of noncash rewards, presumably something like gift cards or credits for other services. The reward must equal at least half the amount saved on average per patient.

That's one area Dr. Thompson says is ripe for abuse. The shared savings could mean a reward of around $900 per dose for a patient who gets Avastin vs. Lucentis or Eylea. He can envision a patient who should get the more expensive drug to preserve her or his vision wanting to stay with the cheaper drug for the reward. "It creates a very perverse incentive," he says.

Quotable

"Failure can be defined in a lot of different ways. I strongly suspect the Medicare Advantage plans are going to struggle coming up with an appropriate definition of failure."

— John Thompson, MD

Another potential problem with step edits, or "fail first": Who defines "failure"? "Failure can be defined in a lot of different ways," Dr. Thompson says. "I strongly suspect the Medicare Advantage plans are going to struggle coming up with an appropriate definition of failure."

IN BRIEF

The Food and Drug Administration granted breakthrough device designation to **Notal Vision** for its home-based optical coherence tomography device. **Notal Home OCT** is a lightweight device designed for technician-free operation by patients with exudative age-related macular degeneration. It uses the **Notal OCT** Analyzer machine-learning algorithm to alert the treating retina specialist of any retinal fluid changes.

Aerpio Pharmaceuticals has completed patient dosing in the TIME-IIb study of AKB-9778 for treatment of severe non-proliferative diabetic retinopathy. The trial is evaluating 167 subjects with moderate to severe NPDR randomized to receive 48 weeks of once- or twice-daily subcutaneous AKB-9778 15 mg or placebo. AKB-9778 binds to and inhibits vascular endothelial protein tyrosine phosphatase, a negative regulator of Tie2.

People with a history of chronic hepatitis B virus infection may be at a higher risk of developing AMD, researchers in Taiwan reported in *Acta Ophthalmologica 2019*. The researchers reported that patients with chronic HBV had a 41 percent greater risk of developing any type of AMD than non-infected patients.

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Strange symptoms point to rare disease

Widefield fluorescein angiography helps arrive at diagnosis after suspicious visual changes.

By David Xu, MD, and Jason Hsu, MD

Department Editor
Jason Hsu, MD

A 42-year-old woman was referred to the retina clinic for evaluation of blurred vision and "blackouts" in both eyes. She had a history of migraines since childhood, which were worsening over the past six months. During this time, she experienced decreased hearing, intermittent vertigo lasting minutes and tinnitus. All of her symptoms had been progressively worsening.

An otolaryngologist performed an audiogram and diagnosed her with otosclerosis. An endocrinologist prescribed her amphetamine/dextroamphetamine for her headaches, but this did not help.

Two months earlier, she had a one-hour episode of dysarthria and arm apraxia, whereupon she presented to the emergency department. Brain computed tomography was normal, and she was diagnosed with a complex migraine.

Workup and imaging findings

At her visit in the retina clinic, visual acuity was 20/40 OD and 20/30 OS. Intraocular pressures were normal. The anterior segment was quiet and unremarkable bilaterally. Fundus examination of the right eye disclosed multifocal yellow intra-arterial plaques (*Figure 1*). The left eye fundus was normal. Widefield fluorescein angiography demonstrated multiple arteriolar occlusions and segmental arteriolar leakage of the right eye and focal non-perfusion of the left eye (*Figure 2, page 12*). The left eye was normal. Optical coherence tomography of the macula was normal bilaterally.

Hospital admission and labs

She was admitted to the hospital. Brain MRI showed a focal hyperintense signal abnormality on the fluid-attenuated inversion recovery (FLAIR) sequence in the corpus callosum, multiple punctate areas of diffusion restriction in the subcortical white mater, and an old right thalamic infarct (*Figure 3, page 12*).

Serum laboratory studies were notable for mildly elevated erythrocyte sedimentation rate of 34 mm/hr., but normal C-reactive protein, blood count and electrolyte levels. Also normal were antineutrophil cytoplastic antibodies, antinuclear antibody, anti-double stranded DNA, complement C3 and C4 level and cryoglobulin testing. Lumbar puncture with cerebrospinal fluid analysis revealed normal chemistry, negative encephalitis panel and no oligoclonal bands.

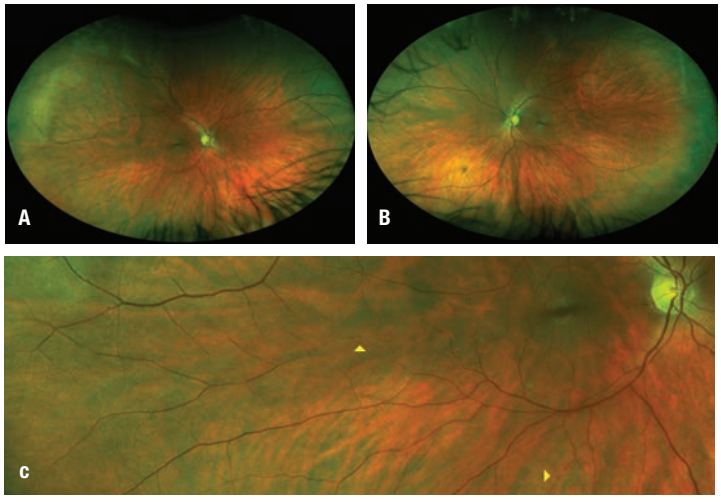

Figure 1. Widefield fundus photographs of the right (A) and left (B) eyes. Higher magnification (C, inset of A) of the right eye discloses two segments of intra-arterial plaques (arrowheads).

Bios

Dr. Hsu is co-director of retina research at Wills Eye Hospital, and associate professor of clinical ophthalmology at Thomas Jefferson University, Philadelphia, and a partner at Mid Atlantic Retina. Dr. Xu is a vitreoretinal fellow at Wills Eye Hospital.

DISCLOSURES: Dr. Hsu and Dr. Xu have no relevant financial relationships to disclose.

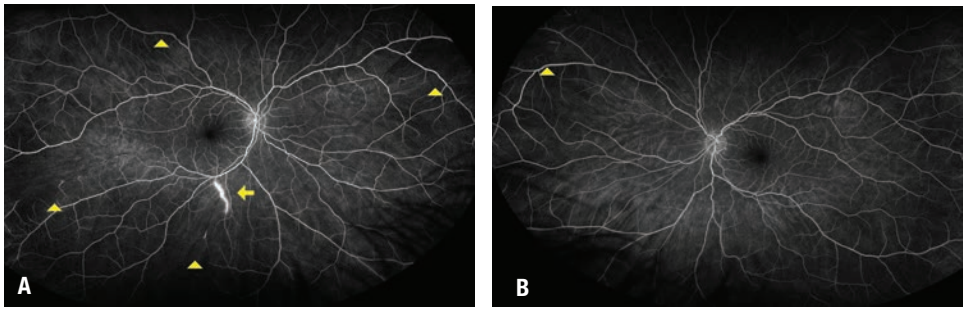

Figure 2. Fluorescein angiogram of the right eye (A) shows arteriolar occlusion in four regions (arrowheads) and arterial wall hyperfluorescence (arrow). The left eye (B) shows focal nonperfusion (arrowhead).

Widefield fluorescein angiography has made the detection of these small branch retinal artery occlusions easier.

The diagnosis is …

Based on the patient's findings, she was diagnosed with Susac syndrome. Her neurologist agreed that the focal hyperintensity in the corpus callosum was consistent with the diagnosis. She began high-dose oral prednisone 100 mg/day on a tapering regimen managed by her neurologist. She also started taking omeprazole and a calcium/vitamin D supplement.

Follow-up

Her headache and tinnitus resolved. She was seen again two months after her initial presentation at which time she was taking prednisone 60 mg/day. Repeat fluorescein angiography demonstrated new areas of arteriolar occlusion and arterial wall hyperfluorescence (AWH) in the right eye and new AWH in the left (*Figure 4*).

She also experienced temporary extremity weakness lasting days each time the prednisone dose was decreased. Because of the incomplete response and high dose of prednisone that was required, mycophenolate mofetil 500 mg b.i.d. was started. She tolerated the medication well and has continued tapering the prednisone with plans for serial follow-up and fluorescein angiography.

The Susac constellation

The constellation of hearing loss, encephalopathy, and branch retinal artery occlusions is the classic triad of manifestations in Susac syndrome.[1] This case highlights many of the characteristic findings of the disease.

Because Susac syndrome is a rare disease, recognizing it requires a high index of suspicion. The condition is often underdiagnosed, in part because the full triad is found only infrequently when the patient first presents.[2] Moreover, BRAOs in these patients may be peripheral and subacute, so patients may not complain of vision loss. Retinal whitening may be absent. Widefield fluorescein angiography has made the detection of these small BRAOs easier.[3]

In 1979, John Susac, MD, and colleagues reported the first series of this condition in two young women who developed subacute progressive neurologic symptoms and multifocal retinal artery occlusions.[4] Based on the ocular findings and brain biopsy of one of the women, which demonstrated angiitis, he concluded the syndrome involved a microangiopathy of the brain and retina.

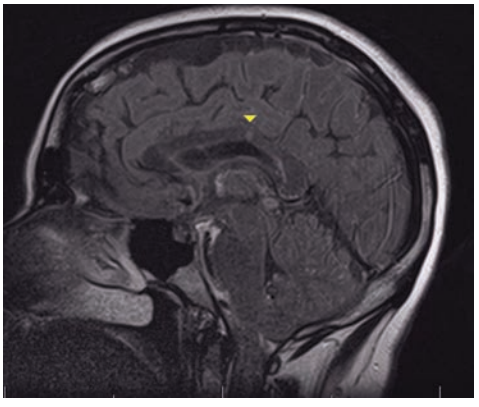

Figure 3. Fluid-attenuated inversion recovery MRI shows a focal hyperintense foci in the corpus callosum (arrowhead).

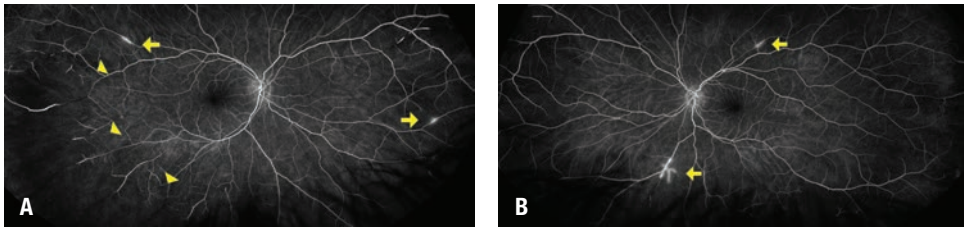

Figure 4. Fluorescein angiogram of the right eye (A) shows increased areas of arteriolar nonperfusion (arrowheads) and new segments of arterial wall hyperfluorescence (AWH, arrow). The left eye (B) also displays new AWH (arrows).

Other telltale signs

In 1986, J. Donald Gass, MD, and colleagues described what we now refer to as Gass plaques, which are yellow arteriolar wall deposits often distributed along the mid-segment of the vessel away from the bifurcation points.[5,6] Another associated finding is arterial wall hyperfluorescence, a prominent feature in our patient, which can be seen on fluorescein angiography and may not necessarily be located near the BRAOs.[7]

Brain lesions tend to include small white matter lesions with a special predilection for the corpus callosum. MRI often shows focal hyperintensity on T2 or FLAIR lesions when they are acute and hypointense holes on T1 imaging when they are chronic.[8] It is important to distinguish these lesions from those of multiple sclerosis because they can both involve the deep white matter, but demyelination is not typical of Susac syndrome.[9]

The exact pathogenesis of Susac syndrome is unclear. It is believed to be an autoimmune process targeting endothelial cells that induce microvascular occlusions of the central nervous system, inner ear and retina. The anti-endothelial response leads to retinal damage ranging from arteriolar plaques to occlusions. Circulating anti-endothelial cell antibodies have been isolated in some patients, but standardized antibody testing has not been developed.[10]

Treatments

The initial treatment is usually systemic intravenous or oral steroids with the goal to stabilize the ocular and neurologic disease.[11] Intravenous immunoglobins have also been used. After treatment of the acute phase, a slow taper of steroid is indicated. Most cases exhibit fairly rapid improvement in headache and neurologic sequelae.

If the disease is persistent or recurrent with steroid tapering, another immunosuppressant such as mycophenolate, azathioprine or cyclophosphamide may be used. Susac syndrome is self-limiting, but it can recur in a minority of patients.

The bottom line

While not all patients have the complete triad on presentation, there are several characteristic findings of Susac syndrome in both the retina and the brain that should prompt evaluation for the disease. It is important for neurologists and otolaryngologists to recognize the disease as well. RS

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Another associated finding is arterial wall hyperfluorescence, which can be seen on fluorescein angiography and may not necessarily be near the BRAO.

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Maculopathy in the middle

This patient with migraines presents with an unusual cause of acute vision loss.

By Brandon Erickson, MD, and Steven S. Saraf, MD

Department Editor
Lisa C. Olmos de Koo, MD, MBA

A 26-year-old Caucasian woman presented to the emergency department with the complaint of vision loss in the left eye for the past three hours. She had a history of typical migraine and had experienced "the most severe episode yet" on the day of presentation.

To help alleviate the headache she had decided to take a nap. Upon awakening, the headache had improved, but she noticed a focal area of vision loss in the superior visual field of her left eye. Her central vision was preserved. She denied flashes, floaters, pain or photophobia.

Medical and ocular history

Her ocular history was unremarkable. Her medical history was significant for migraines starting when she was a teenager, which had not been problematic for many years. She also had anxiety that was treated with Lexapro (escitalopram, Camber Pharmaceuticals). She had stopped the Lexapro a month earlier and noted an increased frequency of migraines that began to occur weekly. She was on the Nexplanon implant (etonogestrel, Merck) for birth control.

Her medical history was also significant for syncope. A previous workup had revealed a "heart murmur with a prolapse." She denied prior episodes of blood clots, miscarriage or familial blood dyscrasias. She denied recent confusion, personality changes, focal neurologic changes or hearing loss. She also denied a history of oral or genital ulcers. She was a non-smoker and used alcohol and marijuana occasionally. She denied cocaine or other illicit drug use.

Retinal whitening on exam

Visual acuity was 20/20 in each eye. Intraocular pressures were normal. Pupils were equal, round and reactive with no relative afferent pupillary defect. Confrontational visual field testing revealed a superotemporal defect in her left eye. Extraocular motility was full and color plates were full in each eye. The slit lamp examination was within normal limits in both eyes. Dilated fundus exam in the left eye was notable for retinal whitening in the inferior macula extending along the inferotemporal arcade. No intra-arterial emboli or plaques were seen.

OCT finds lesions, edema

Neurology conducted a workup in the ED to evaluate for a source of embolism and stroke. This included CT of the head and neck with angiography, brain MRI and echocardiography, all of which

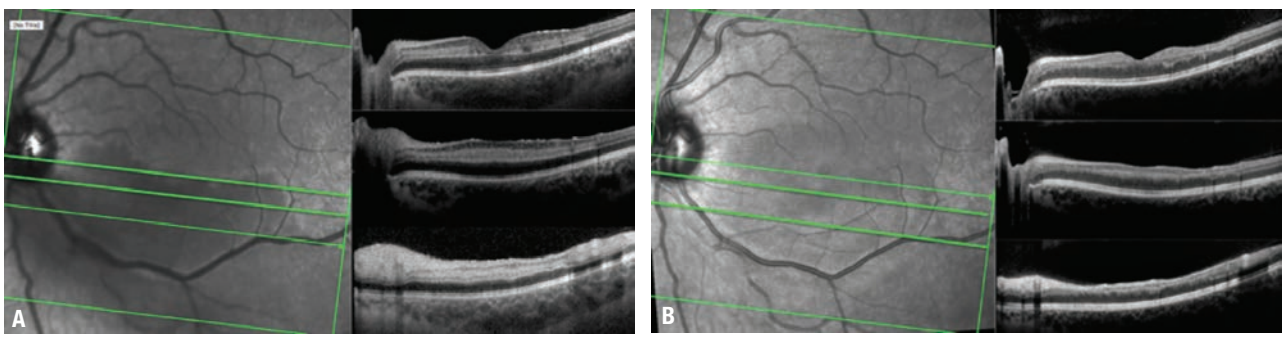

Figure 1. Spectral domain optical coherence tomography at presentation shows hyper-reflective bands abutting the inner nuclear layer (A) and mild thinning and atrophy of middle retinal layers one month later (B).

were normal. A broad laboratory workup was unrevealing, with normal/negative findings for partial thromboplastin time, antinuclear antibody, syphilis serology, quantiferon gold, proteinase 3 antibody, myelperoxidase antibody, homocysteine, antiphospholipid antibody, protein C/S activity, antithrombin activity, prothrombin activity, cryoglobulins, serum protein electrophoresis, complete blood count, comprehensive metabolic panel and urinalysis.

Fluorescein angiography revealed no focal vasculitis or ischemic changes. The vessels in the left eye had a normal transit time and filled evenly. Fundus photography of the left eye revealed whitening along the inferior arcade extending up to but sparing the fovea. Optical coherence tomography of the left macula revealed hyper-reflective band-like lesions at the inner nuclear-layer level in addition to inner retinal edema along the inferior arcade consistent with loss of inner retinal circulation (*Figure 1A*).

Diagnosis and management

The patient was diagnosed with branch retinal artery occlusion with the associated finding of paracentral acute middle maculopathy (PAMM) extending to the parafoveal region. The close temporal proximity of the vision loss to the patient's "most severe migraine headache to date" was suspicious for a possible connection between the two processes.

The goal of management was to prevent future similar episodes, which prompted the extensive laboratory workup. We counseled her that her visual field loss may improve, but that it may also have an irreversible component. We also suggested she avoid estrogen-containing hormonal contraceptives and smoking, given the demonstrated propensity for possible thrombotic events. She decided to discontinue her progesterone-based contraceptive on her own.

After discussion with her neurologist, she was also started on topiramate as prophylaxis against future migraine episodes.

We reexamined the patient one month later, and the first follow-up OCT showed atrophic thinning of the affected retina (*Figure 1B*).

Findings in the middle retinal layer

In 2014 Suqin Yu, MD, and colleagues described abnormal bands of hyperreflectivity on spectral domain OCT as a marker of retinal ischemia, with hyperreflectivity of the superficial capillary plexus corresponding to cotton wool spots, and hyper-reflective bands in the middle retinal layer corresponding to deeper foci of retinal whitening.[1] In 2015 David Sarraf, MD, and colleagues described similar hyper-reflective bands in the middle retinal layers on OCT that lacked angiographic correlation, which have since been termed PAMM.[2,3]

PAMM is a finding on SD-OCT characterized by hyper-reflective band-like lesions at the inner nuclear layer in patients with an acute negative scotoma. The retinal capillary network is composed of the superficial capillary plexus, located at the ganglion cell layer and the intermediate and deep capillary plexuses at the level of the inner nuclear layer.

Pathophysiologically, PAMM is thought to result from localized retinal capillary ischemia at the level of the intermediate or deep plexuses, resulting in localized edema surrounding the inner nuclear layer.[4,5] OCT angiography has produced new insights into both retinal vascular anatomy and clinical correlations when select structures are affected, such as in PAMM.[6] In this condition, deep capillary plexus abnormalities appear on OCTA.

Analogous to cotton wool spot

The presence of PAMM serves as a sign of an underlying vascular disease. It is not considered a diagnosis, analogous to a cotton wool spot. It has been reported in patients with BRAO, central retinal vein or artery occlusion, diabetic

The goal of management was to prevent future similar episodes, which prompted the extensive laboratory workup.

UW Medicine EYE INSTITUTE

Dr. Olmos de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Dr. Erickson is a second-year ophthalmology resident and Dr. Saraf is a retina fellow.

retinopathy, hypertensive retinopathy, sickle cell retinopathy, Purtscher's retinopathy, retinal vasculitis, carotid embolism, migraines, medication toxicity, hypovolemia, orbital compression injury and viral illness.[4,8]

The designation of PAMM is made on the basis of a combination of a clinical history of acute scotoma with the described SD-OCT findings. PAMM lesions may be seen on fundus examination as whitish parafoveal deep retinal lesions that are smoother and more grayish than cotton wool spots. Patients with vascular risk factors typically present in their 50s or 60s. In younger patients, however, PAMM is often idiopathic. Although there is no specific treatment for PAMM, it is important to take a thorough history and appropriately work-up patients to rule out systemic contributions.[4]

Pay attention to findings of hyper-reflectivity of the middle retinal layers on OCT.

Follow-up and bottom line

One month after her initial presentation, our patient still noticed the "blind spot" present in her initial visit, although she characterized it as lighter and less opaque. Typically, a partial scotoma is the usual outcome in these patients, and they should be counseled accordingly.[8,11]

Our patient highlights the importance of recognizing PAMM in cases of unexplained vision loss. In particular, pay attention to findings of hyper-reflectivity of the middle retinal layers on OCT. Although no definitive evidence links migraine with BRAO or PAMM, prior case reports have demonstrated a similar clinical experience.[8,12] Future studies utilizing OCTA and other imaging modalities may help us to better understand the responsible vascular alterations, particularly if captured in the acute setting.

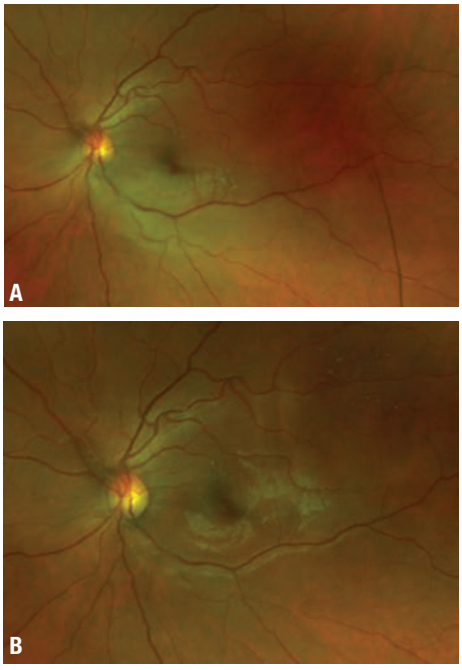

Figure 2. Fundus photography at presentation (A) shows retinal edema along the inferior arcade with retinal whitening extending up to the parafoveal region. At one month follow-up (B), the edema resolved and vascular attenuation of the arteries of the inferior arcade increased.

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Retina Specialist Online

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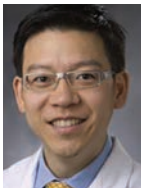
A far reach: PPV in highly myopic eyes

Pearls for performing a pars plana vitrectomy in pathologic myopia.

By Tatsuhiko Sato, MD, and Michael A. Klufas, MD

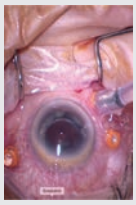


Department Editor
Paul Hahn, MD, PhD

You see the thick glasses. The globe looks like an egg that is about to burst. Pathologic myopia can make any retina specialist nervous, especially when surgery is indicated. Highly myopic eyes are not uncommon in the retina clinic.

Here, Michael A. Klufas, MD, of Wills Eye Hospital and Tatsuhiko Sato, MD, of Hayashi Eye Hospital in Japan provide their pearls for operating on these challenging eyes.

View the Video



Murtaza Adam, MD, and James Vander, MD, of Wills Eye Hospital repair a myopic macular detachment secondary to a macular hole. Available at: bit.ly/VideoPearl_009

Anesthesia

Myopic eyes may have a posterior staphyloma. Consider appropriate local anesthesia techniques to prevent inadvertent globe perforation. If you're not so familiar with retrobulbar block in high-myopia cases, we recommend a peribulbar injection or sub-Tenon's block.

Reach

Preoperatively, axial length measurement (>30 mm) can be helpful to determine if special instrumentation will be required, such as extra-long forceps. For

(Continued on page 38)

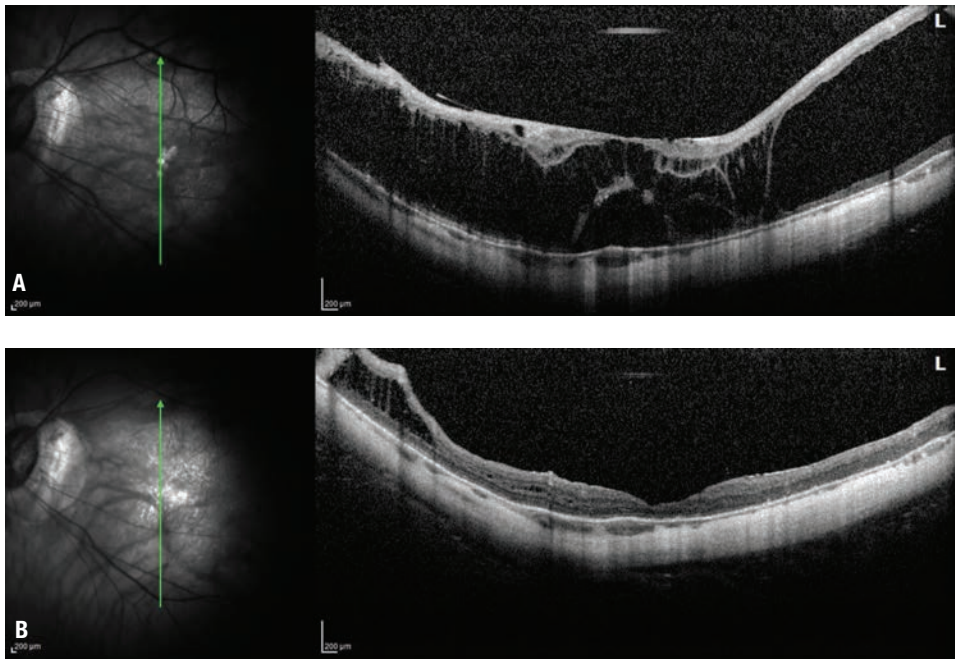


Figure. A 59-year-old, phakic -20 D myope presented with progressive myopic schisis without macular hole in the left eye (A). Preoperative vision was 20/300. After pars plana vitrectomy with internal limiting membrane peeling and gas tamponade (B), the macular schisis resolved and vision at one-year follow-up after phacoemulsification was 20/60.

Bios

Dr. Hahn is a partner at New Jersey Retina in Teaneck. Dr. Sato is with Hayashi Eye Hospital in Fukuoka, Japan. Dr. Klufas is with the retina service of Wills Eye Hospital and assistant professor of ophthalmology at Thomas Jefferson University, Philadelphia.

DISCLOSURES: Drs. Sato and Klufas have no relevant relationships to disclose.
Dr. Hahn disclosed he is a consultant to Alcon.

KNOW THE HAZARDS THAT LURK AT 'CELL THERAPY' CLINICS

Commercial clinics peddle unproven therapies that have harmed patients. Retina specialists have a duty to educate their patients about these hazards.


Rajinder S. Nirwan, MD


Daniel Simhaee, MD


Ajay E. Kuriyan, MD, MS


Thomas A. Albini, MD

By Rajinder S. Nirwan, MD, Daniel Simhaee, MD, Thomas A. Albini, MD, and Ajay E. Kuriyan, MD, MS

Take-home points

- "Cell therapy" clinics advertise unproven and sometimes harmful treatments directly to consumers via websites.
- These websites tend to overemphasize benefits and minimize potential risks.
- For retinal diseases, the literature reports more complications from these treatments than positive outcomes.
- Retina specialists have a role to educate the public about the potential risks of these "cell therapy" clinics.

Bios

Dr. Nirwan is a resident at Flaum Eye Institute, University of Rochester (N.Y.) Medical Center, and will start a fellowship in vitreoretinal surgery at the University of Calgary, Alberta, in July.

Dr. Simhaee is a vitreoretinal surgery fellow at Flaum Eye Institute.

Dr. Kuriyan is an assistant professor at Flaum Eye Institute.

Dr. Albini is a professor of clinical ophthalmology at Bascom Palmer Eye Institute, University of Miami.

Cell therapy has the potential to treat a diverse set of refractory medical conditions. It has already been integrated into many medical disciplines and has proven to be efficacious in the regular management of various hematologic diseases.[1–3]

Multiple clinical trials are investigating cell therapy for ophthalmologic conditions, including age-related macular degeneration, diabetic retinopathy, hereditary retinal degenerations and retinal vein occlusions, according to a search on ClinicalTrials.gov.[4] Some trials have already been completed.

However, commercial "cell therapy" clinics threaten to undermine both scientific progress and public trust in stem-cell research. This article explores the state of legitimate research into cell therapy treatments for retinal diseases as well as the scope of the less credible commercial "cell therapy" clinics.

Scientifically rigorous studies

Recently, promising outcomes from scientifically rigorous studies have demonstrated safety and positive anatomic and visual changes following subretinal transplantation of human embryonic stem cell-derived retinal pigment epithelium cells for Stargardt's macular dystrophy and AMD.[5] This safety profile of stem-cell therapy has been paralleled by other published studies, with both dissociated cells and stem cell-derived RPE sheets.[6–9]

Studies implanting subretinal stem cell-derived RPE sheets in eyes with neovascular and non-neovascular AMD have demonstrated stabilization of vision loss, with a few patients even exhibiting improvement in vision.[7–9] Optical coherence tomography imaging has revealed changes consistent with monolayer and host photoreceptor integration.[9]

Comparably, the subretinal delivery of a single dose of human umbilical stem cells in eyes with geographic atrophy secondary to AMD had no episodes of immune rejection or tumor formation and showed some improvement in visual acuity.[6] A relatively high rate of retinal perforation and detachments was attributed to the trans-scleral delivery technique.

Studies have shown early efficacy, stability and functional improvement without significant adverse effects. These results have fortified optimism not only for the research community, but also for patients with progressive, end-stage retinal diseases. Meticulous scientific studies of cell therapies continue to provide evidence to propel these treatments forward.

'Cell therapy' clinics gain foothold

However, in recent years commercial "cell therapy" clinics have advertised treatments for a multitude of diseases, including ocular conditions, although none of these clinics have been approved by the Food and Drug Administration.

Access to these clinics is readily available to patients through direct-to-consumer online marketing. Some of these clinics list trials on Clinicaltrials.gov. However, most patients are unaware that Clinicaltrials.gov is a repository for ongoing clinical trials rather than an endorsement of specific clinical trial studies.

The concern of these "cell therapy" clinics targeting various medical conditions has gained international attention, especially following reports of major complications. They include glioproliferative lesions of the spinal cord after intrathecal stem-cell infusions in China, Argentina and Mexico.[10]

"Cell therapy" clinics are not limited to outside the United States. A 2016 study found 187 U.S. websites offering cell therapy for various diseases at 215 different clinics.[11] A similar study found 351 companies in the United States with as many as 570 clinics that market cell therapy direct to consumers.[12]

Our study of commercial clinics

We performed a study to assess U.S.-based companies with websites that promoted online, direct-to-consumer access to "cell therapies" for ocular disease. From our search, we discovered approximately 40 companies that do so for ophthalmic conditions at 76 clinics across the country.

The exterior of the U.S. Stem Cell Clinic office in Sunrise, Fla., which was the subject of a warning letter from the Food and Drug Administration and of a *New England Journal of Medicine* article that reported on three patients who went blind after treatments. (Jim Rassol / South Florida Sun Sentinel / Polaris).

These clinics offer interventions for a wide range of ocular conditions, most commonly macular degeneration, optic neuritis, retinitis pigmentosa and diabetic retinopathy. In regards to the source of "cell therapy" they use, the overwhelming majority are autologous-based treatments, with a small number offering allogenic-based treatments.

The most frequently advertised "cell therapy" source is autologous adipose-derived stem cells, while less common sources include autologous bone marrow-derived stem cells, amniotic stem cells, peripheral blood-derived stem cells, umbilical cord blood stem cells, placental stem cells, allogenic bone marrow-derived stem cells and xenocells.

Where's the evidence?

Most companies did not advertise the specific modes of "cell therapy" delivery. Among those that did, the most common route of administration was intravenous. Ocular-specific "cell therapy" delivery processes include "eye injection,"

(Continued on page 22)

Disclosures

Dr. Kuriyan is a consultant to Regeneron, Valeant, Alimera Sciences and Allergan, and receives grant funding from Second Sight.

Dr. Albini is a consultant to Janssen, Genentech and Notal Vision.

Drs. Nirwan and Simhaee have no relationships to disclose.

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

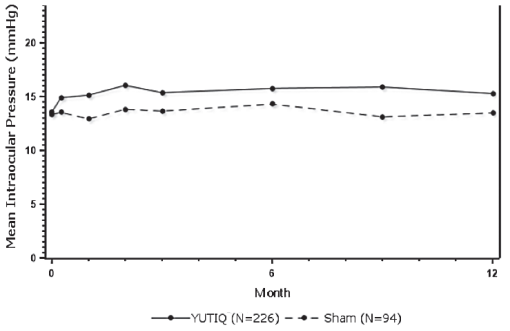
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

INTRODUCING

YUTIQ™
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover continuous calm in uveitis

New YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg

Designed to deliver a sustained release of fluocinolone for patients with chronic noninfectious posterior uveitis for up to 36 months[1]

- 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.]
- Extended median time to first recurrence of uveitis[1,2]
  [At 12 months–NE† for YUTIQ/92 days for sham in study 1; NE for YUTIQ/154 days for sham in study 2.]
- Mean intraocular pressure (IOP) increase was comparable to sham[1,2]
  Study was not sized to detect statistically significant differences in mean IOP.

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 need for rescue medications.
†NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

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

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

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

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

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

Adverse Reactions

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

References: 1. YUTIQ™ (fluocinolone acetonide intravitreal implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** Data on file.

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

EYEPOINT™ PHARMACEUTICALS

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12/2018
YUT00009

(Continued from page 19)
intravitreal injection, retrobulbar injection, eye drops, retrofundal injection, sub-Tenon's injection and intraocular injection with vitrectomy. The cost for these treatments ranged from $4,000 to $10,500, although some reports have listed prices upwards of $50,000.[13]

We also studied the level of scientific evidence for treatments at these clinics for retinal diseases. We performed a PubMed search and classified publications from these "cell therapy" clinics using the Oxford Centre Level of Evidence (*Table*). We found a paucity of publications supporting these treatments: no level 1, 2, 3 or 4 evidence. There was one case report (level 5 evidence) of a patient with serpiginous choroidopathy who was treated with intravitreal bone marrow-derived stem cells and was reported to have an improvement in vision.[14]

The cost for these treatments ranged from $4,000 to $10,500, although some reports have listed prices upwards of $50,000.

Given the paucity of publications from commercial cell therapy clinics, we examined their websites to see whether they advertised any evidence of their treatments. Although we didn't find information about numbers of patients treated and specific outcomes, nearly half (43 percent) of the websites suggested or explicitly claimed "clinically significant benefits" from their treatments.

Thirty percent claimed that their treatments would be better than the standard of care for conditions such as macular degeneration. Nearly half (43 percent) of the websites did not list any risks from the treatments, and 20 percent listed only "minor risks." Furthermore, only half of the websites acknowledged that these treatments are experimental.

Disastrous outcomes

The positive outcomes with minimal risks touted by the cell therapy clinic websites are in stark contrast to the reports of severe, blinding complications from their treatments.

The most notable publication to date is a case series of three patients with macular degeneration who were treated at a single clinic in Florida with bilateral intravitreal injections.[15] Five of the six treated eyes went on to develop retinal detachments with proliferative vitreoretinopathy.[15] The vision in those patients deteriorated from 20/30 to 20/50 in their better-seeing eye before treatment to 20/200 to no light perception afterward.

Another case report described a patient with macular degeneration who had bilateral intravitreal injections at a different clinic and then developed bilateral retinal detachments with severe proliferative vitreoretinopathy.[16] The patient's vision worsened from 20/400 to hand motion in the right eye and 20/200 to LP in the left.

A subsequent case report involved a patient with Stargardt's disease who received a subretinal injection of bone marrow-derived stem cells and developed a retinal detachment.[17] The patient's vision deteriorated from 20/400 to HM before having RD repair, which restored his vision to his baseline.

Call for increased regulation

The severity of these complications points to a need for increased regulation of these clinics. They claim to bypass FDA regulation by reasoning that cells are minimally manipulated and are utilized for homologous use.

The FDA responded by issuing draft guidance statements in December 2014 and October 2015, updated in December 2017, defining the term "minimally manipulated" stem cells to delineate homologous use.[18,19] This was done to delineate that autologous stem cells and their application fall under the regulatory oversight of the FDA.

In 2016 the American Academy of Ophthalmology issued a clinical statement underscoring that no FDA-approved stem-cell therapies exist for ocular conditions, and that the risks associated

with such treatments are unknown.[20] Due to the concern for lack of evidence of safety and tissue handling, the FDA has begun issuing warnings to various clinics in an effort to address this problem.[21]

Patients need education

Although cell therapy has the potential to have a significant impact on retinal diseases, it's important that patients understand the current limitations of treatment and receive education about the potential complications from treatments at these commercial "cell therapy" clinics.

Patients should be educated to avoid "cell therapies" that require out-of-pocket payment, offer bilateral treatments, and are done by centers that provide only "cell therapy" treatments.

Legitimate scientific cell-therapy clinical trials are typically sponsored by either the government or companies and don't ask for payment out-of-pocket. Legitimate clinical trials don't perform bilateral simultaneous treatments until safety has been demonstrated. Lastly, these scientific studies are carried out by retina specialists who can provide other treatments for early stage disease, such as anti-VEGF for exudative macular degeneration.

Table. Oxford Centre for Evidence Based Medicine levels of evidence[22]

Level	Nature of evidence
1a	Systematic review (with homogeneity) of randomized clinical trials
1b	Individual RCT (with narrow confidence interval)
1c	All or none (i.e., all patients died before treatment became available, but some now survive; or when some patients died before treatment became available, but none now die from it)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (low-quality RCT; e.g., <80 percent follow-up)
2c	"Outcomes" research or ecologic studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion, or based on physiology, bench research or "first principles."

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Legitimate scientific cell therapy clinical trials are typically sponsored by either the government or companies.

Current and new steroid therapy in NONINFECTIOUS UVEITIS

Corticosteroid therapy is the cornerstone of treatment. Sustained delivery systems and concomitant use with other medications are expanding options.

Thomas A. Albini, MD

Justin Yamanuha, MD

By Thomas A. Albini, MD, and Justin Yamanuha, MD

Take-home points

- Optical coherence tomography and angiography will help to classify the primary site of ocular inflammation.
- Topical corticosteroids can be initiated early in the course of uveitis and can quickly be tapered or discontinued as needed.
- Treat infectious causes concomitantly with appropriate antibiotic, antiviral, antifungal or antiparasitic therapy.
- Periocular and intravitreal corticosteroids are options when topical therapy is insufficient.

Corticosteroids are often the primary treatment for noninfectious uveitis, administered via either the topical, regional or systemic routes. Many retina specialists are utilizing intravitreal corticosteroids as adjuncts to anti-VEGF injections in diabetic macular edema and cystoid macular edema secondary to retinal vein occlusions.[1]

Regional steroids in noninfectious uveitis can effectively treat intraocular inflammation and uveitic macular edema, but their use is perhaps more nuanced and less algorithmic than in other conditions. We outline some guidelines for retina specialists treating noninfectious uveitis to help optimize safety and efficacy while reducing complications, and then we review the available and investigative therapies.

Ensuring the correct diagnosis

Following a careful targeted history and anterior segment and fundus examinations, ocular imaging with optical coherence tomography and angiography will help to classify the primary site of inflammation and can aid in making a diagnosis. Retina specialists should employ a tailored laboratory evaluation for possible systemic inflammatory and especially infectious laboratory workup in all cases of posterior segment-involving uveitis.

If the diagnosis is unclear or if the prescribed treatment has not produced the expected outcome, referral to a uveitis specialist can help direct care,[2] particularly when considering systemic treatment with immunosuppressive or biologic therapy (i.e., anti-tumor necrosis factor agents). The use of systemic therapy is beyond the scope of this targeted review.

Starting topical corticosteroids

Topical corticosteroids such as prednisolone acetate can usually be initiated early in the course of uveitis, and can quickly be tapered or discontinued if necessary. Infectious causes should be concomitantly treated with appropriate antibiotic, antiviral, antifungal or antiparasitic therapy.

Prednisolone acetate and similar topical corticosteroids will not penetrate the posterior segment in adequate concentrations to resolve vitreous inflammation,

Bios

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Dr. Yamanuha has no relationships to disclose.

so these are typically insufficient as the primary therapy for intermediate or posterior uveitis. Fluorinated topical steroids such as difluprednate acetate (Durezol, Novartis)[3] allow for better penetration into the posterior segment and can be very effective at improving vitreous cells, vitreous haze, and mild uveitic macular edema (UME). These potent corticosteroids also have an increased risk of steroid-induced intraocular pressure and cataract progression, so use them with caution.

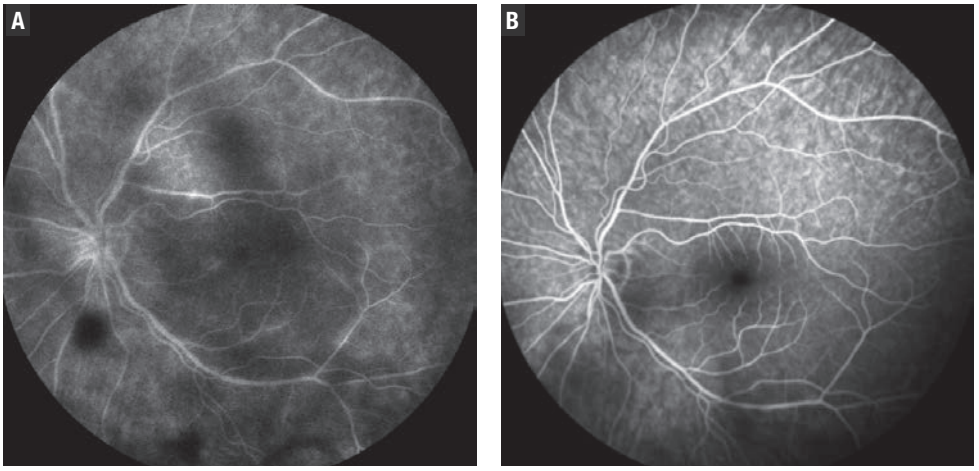

Figure. Fluorescein angiograms show vascular leakage before sub-Tenon's injection of Kenalog (A) and resolution of much of the leakage after injection (B).

Transitioning to regional corticosteroids

If topical corticosteroids are insufficient to improve inflammation, or if structural complications such as UME arise, regional corticosteroids can be useful adjunctive or primary treatments.

Again, give consideration to appropriate anti-infective treatments if necessary, because regional steroids can worsen an infection not treated completely, and they are more difficult to discontinue once administered.

The next steps in transitioning to regional corticosteroids are:

- determining the location (periocular vs. intraocular); and
- the desired duration of effect (from months to potentially years).

Periocular corticosteroids

Triamcinolone acetonide (Kenalog, Ranbaxy Laboratories) delivered into the sub-Tenon's space or through the orbital septum is a readily available, cost-effective option for treating noninfectious uveitis. The most common concentration is 40 mg/mL (i.e., Kenalog-40). It's typically delivered in 0.5-mL volumes.

Sub-Tenon's triamcinolone would typically have a duration of two to three months, and the location provides a depot for slow release of steroid over this interval. Because the crystal sizes are variable in Kenalog suspensions, the duration of action may not be identical even if both eyes are treated from the same vial. Complications can include ptosis, ocular hypertension and cataract.

Intravitreal steroids: short- vs. long-acting

The decision to use an intravitreal steroid may follow administration of a periocular steroid, or if it's indicated to rapidly resolve intermediate or posterior uveitis with associated UME. Triesence (Alcon),[4] preservative-free triamcinolone acetonide, is a single-use injectable suspension designed for intraocular use. While the concentration is similar to its preserved counterpart (40 mg/mL), a typical intravitreal injectable dose would be 4 mg/0.1 mL. It's usually administered inferotemporally.

Check IOP immediately after injecting Triesence because the medication can produce a sudden spike. Because the crystals in Triesence are uniformly sized, it has a predictable duration of action of roughly four to six weeks. The one caveat is that

Check IOP immediately after intravitreal Triesence injection because it can produce a sudden spike.

Triesence crystals may clear more rapidly out of a vitrectomized eye than in an eye with intact vitreous.

Retisert

This sutured, surgically implanted fluocinolone implant (Bausch + Lomb) has been in use since 2005 and has been extensively studied. Most recently, the seven-year follow-up data of the MUST trial revealed that the implant performed as well as the systemic therapy over the first five years.[5] However, the implant has also had significant local complications, including the need for cataract surgery in most patients and glaucoma surgery in up to 40 percent of patients.

Ozurdex

Ozurdex (dexamethasone intravitreal 0.7-mg implant, Allergan) is approved for noninfectious uveitis.[6] Retina specialists may comfortably incorporate Ozurdex injections because they are routinely used for diabetic macular edema and retinal edema secondary to retinal vein occlusions along with anti-VEGF injections.

Ozurdex implants should not be used if the posterior capsule was disrupted in cataract surgery, but they can be safely used in patients who have had a YAG capsulotomy.

Ozurdex injections are given via a beveled entry into the sclera with a 25-gauge injector system. IOP rise predictably occurred at four to six weeks in most of the clinical studies, so this provides a convenient time frame in which to see a patient in follow-up. Avoid these injections if the posterior capsule had been disrupted in cataract surgery, but they can be safely used in patients who have had a YAG capsulotomy.

The duration of action of Ozurdex is typically three to four months. The POINT trial,[7] a recent prospective randomized comparative study of intravitreal triamcinolone, Ozurdex and sub-Tenon's triamcinolone for UME, determined both intravitreal injections had a greater and faster therapeutic effect compared with sub-Tenon's injections, but found no significant differences between the two intravitreal injections.

Yutiq

Yutiq (0.18-mg fluocinolone acetonide intravitreal implant, EyePoint Pharmaceuticals) received Food and Drug Administration approval in October 2018 for the treatment of noninfectious posterior segment uveitis.

This implant is virtually identical to the Iluvien implant (0.19 mg fluocinolone acetonide, Alimera Sciences) approved for the treatment of diabetic macular edema in the United States and Europe, and for noninfectious uveitis in Europe.[8]

Yutiq releases approximately one-third the dose of Retisert over roughly the same duration—three years.

A one-year confirmatory study of the ability of the Yutiq implant to reduce uveitis recurrences showed that, compared to sham injections, Yutiq-treated patients were roughly half as likely to experience recurrence of posterior uveitis requiring steroid rescue or systemic treatment at one year—32.7 percent in fluocinolone acetonide treated eyes vs. 59.6 percent in sham-treated eyes.[9]

Suprachoroidal triamcinolone

A novel development from Clearside Biomedical is Xipere, previously known as CLS-TA, a proprietary delivery system of triamcinolone acetonide into the suprachoroidal space.

The Phase III PEACHTREE trial evaluated the company's suprachoroidal triamcinolone acetonide platform in patients with macular edema secondary to noninfectious uveitis.[10] The study showed that significantly more patients gained 15 letters in the Xipere-treated group (47 percent) compared with controls (16 percent) at six months ($p < 0.001$).

The CLS-TA group also had a 50-percent reduction of macular edema, and the vast majority (85 percent) didn't require rescue therapy during the six-month study period. This may one day provide an approved delivery system for uniform periocular

(Continued on page 38)

PRP vs. anti-VEGF for DR patients lost to follow-up

After LTFU, visual acuity worsens in both anti-VEGF and PRP groups, but recovers somewhat in the former.

By Daniel Su, MD, Anthony Obeid, MD, MPH, and Jason Hsu, MD

Daniel Su, MD

Anthony Obeid, MD, MPH

Jason Hsu, MD

Take-home points

- Panretinal photocoagulation group had a loss-to-follow-up (LTFU) duration that was 28 percent longer.
- After LTFU, visual acuity in both anti-VEGF and PRP groups worsened significantly.
- After additional therapy, visual acuity in the PRP group eventually returned to baseline.
- The anti-VEGF group had significantly higher rates of tractional retinal detachments.

The Diabetic Retinopathy Clinical Research Network Protocol S trial demonstrated that ranibizumab (Lucentis, Roche/Genentech) monotherapy was non-inferior to panretinal photocoagulation at two years in terms of visual acuity outcomes.[1] More recently in 2017, the CLARITY trial in the United Kingdom showed us for the first time that aflibercept (Eylea, Regeneron) monotherapy delivered superior VA outcomes at one year compared to PRP.[2]

In addition, PRP has several potential side effects, including reduced peripheral and night vision, worsening of diabetic macular edema and decreased contrast sensitivity.[3–5] Because of these findings, the use of anti-VEGF monotherapy for these patients has gained interest.

LTFU trends for anti-VEGF vs. PRP

Data from clinical trials often do not translate into real-world outcomes, especially in a patient population for whom adherence to treatment recommendations can be challenging. Our institution recently looked at rates of lost to follow-up (LTFU) in 2,302 patients with proliferative diabetic retinopathy after receiving either anti-VEGF vs. PRP.[6]

We found that about a quarter of patients with PDR were LTFU after at least one treatment session for a year or more. We identified some risk factors for LTFU in this study (*see "Why PDR Patients May Not Come Back," November 2018* Retina Specialist), but the study also raised two important questions:

- What happened to these patients when they returned to our office?
- Was there a difference in outcome if they had received only anti-VEGF vs only PRP?

Therefore, we conducted a study that sought to evaluate the outcomes between eyes that received only anti-VEGF therapy vs. PRP and were LTFU for more than six months after their procedure.

Characteristics of LTFU population

Seventy-six eyes were eligible for inclusion in our study. Thirty eyes received

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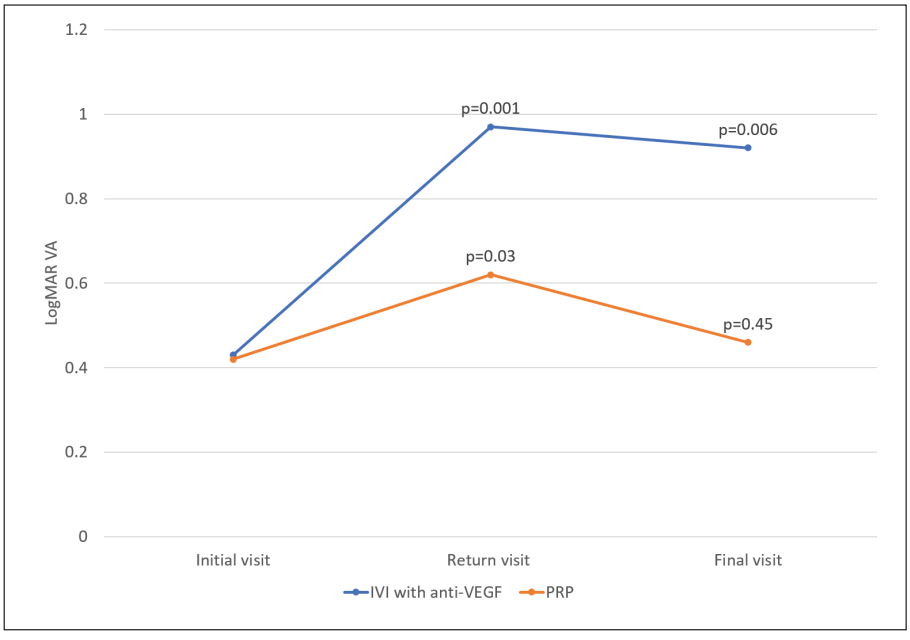

Figure. At the visit before patients were lost to follow-up (LTFU), visual acuity in both the anti-VEGF and panretinal photocoagulation groups were about the same. On the return visit after LTFU, VA worsened significantly in both groups, but eventually returned to baseline in the PRP group. (Used with permission Obeid A, Su D, Patel SN, et al. Ophthalmology. 2018 August 2. [Epub ahead of print]).

Bios

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DISCLOSURES: Drs. Su and Obeid have no relationships to disclose. Dr. Hsu disclosed receiving grants from Roche/Genentech, Santen and Ophthotech. He also receives personal fees from Ophthotech and serves as a consultant for UCB.

anti-VEGF and 46 received PRP prior to LTFU. Of those that received anti-VEGF, 11 received bevacizumab (Avastin, Roche/Genentech), five ranibizumab and 14 aflibercept. The anti-VEGF group received a mean of five injections prior to LTFU, and the PRP group received a mean of two PRP sessions.

The mean duration of LTFU was 371 days for the anti-VEGF group and 465 days for the PRP group. After returning from LTFU and resuming therapy, the anti-VEGF group received an average of four additional injections and one PRP session between the return visit and the final visit. The PRP group received an average of one injection and one additional PRP session between the return and final visit.

Anatomic, visual outcomes

At the visit prior to LTFU, visual acuity in both groups were very similar (20/53; *Figure*). After being LTFU, VA worsened significantly in both groups (20/187 for anti-VEGF and 20/83 for PRP). However, VA in the PRP group eventually returned to baseline (20/58) after additional therapy, while VA in the anti-VEGF group remained significantly worse compared to baseline (20/166).

Due to the retrospective nature of the study and current practice patterns, this is in the context of a higher proportion of eyes with DME in the anti-VEGF group at all three time points (86 percent in the anti-VEGF group vs. 16 percent in the PRP group at baseline).

In terms of other anatomic outcomes, the presence of vitreous hemorrhage was similar between the two groups at all three study time points. Thirteen percent of eyes in the anti-VEGF group required vitrectomy for vitreous hemorrhage vs. 9 percent in the PRP group.

Most striking finding

Perhaps the most striking outcome of this study is the difference in the incidence of tractional retinal detachments (TRD) and neovascular glaucoma (NVG) between the two groups. At the visit prior to LTFU, there was one TRD in the anti-VEGF group and none in the PRP group. At the return visit, 17 percent of eyes in the anti-VEGF group developed a TRD (which increased to more than 30 percent of eyes

How we designed this LTFU study

This was a retrospective cohort study performed at Mid Atlantic Retina, with offices in Pennsylvania, New Jersey and Delaware, and the Retina Service of Wills Eye Hospital, Philadelphia.

We identified eyes diagnosed with proliferative diabetic retinopathy between September 2013 and September 2016 that had received either anti-VEGF therapy or panretinal photocoagulation and were then LTFU for at least six months immediately after treatment.

We excluded eyes with a history of neovascular age-related macular degeneration, retinal vein occlusion, uveitis, or a history of prior treatment with a different provider. In the PRP cohort, we excluded eyes that had received anti-VEGF less than three months prior to PRP. In the anti-VEGF cohort, we excluded eyes with any prior PRP.

We analyzed three major time points:

- The visit just before LTFU, when either intravitreal anti-VEGF injection or PRP was performed.
- The return visit (at least six months after LTFU).
- The final visit.

At each time point, we analyzed the functional outcome in terms of VA and anatomic outcomes in terms of the presence of macular edema, vitreous hemorrhage, tractional retinal detachments and neovascular glaucoma.

by the final visit). In comparison, no eyes in the PRP group had a TRD at the return visit and only one eye (2 percent) had a TRD by the final visit.

This translates to around 20 percent of eyes requiring vitrectomy for TRD repair in the group treated with anti-VEGF vs. none in the group treated with PRP. There were also four cases of iris neovascularization with two developing NVG in the anti-VEGF group by the final visit vs. none in the PRP group.

Bottom line

While anti-VEGF injections may deliver superior visual outcomes when follow-up is consistent, this is not always feasible in the real world where patients in this population are at particularly high risk of being LTFU for prolonged time periods. This is especially concerning given that the effect of anti-VEGF may only last one month after intravitreal delivery.[7]

On the other hand, PRP is known to have a long-term effect. More than 80 percent of eyes in the Early Treatment Diabetic Retinopathy Study retained 20/40 or better vision after 16.5 years of follow up.[8]

When determining the choice of treatment, clinicians must weigh the benefit of anti-VEGF monotherapy against the risk of potentially vision-threatening outcomes if the patient fails to follow up.

In the future, longer acting anti-VEGF therapies or delivery systems may eventually sway the treatment paradigm toward anti-VEGF monotherapy, but for now therapy with PRP may be more protective long term in case patients are LTFU.

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Perhaps the most striking finding of this study is the difference in the incidence of TRD and NVG between the two groups.

Pipeline Update

20 milestones ahead in AMD, DME meds

A look at chemical and biologic agents queued this year or next for key steps toward commercialization.

By Richard Mark Kirkner, Editor

Take-home Points

- Developers of 20 investigative treatments for age-related macular degeneration or diabetic eye disease, or both, expect to achieve important milestones in 2019.
- The list includes four new entries and four drugs have been dropped from the list.
- One potential blockbuster and a prefilled syringe are scheduled to enter the market in 2019.

Expert commentary

"2019 will see the recruitment of multiple Phase III trials in diabetic macular edema, wet age-related macular degeneration and geographic atrophy, outcomes of which have the potential to change how we manage these diseases. Within the first few months of 2019, I'm looking forward to readouts of DRCR network Protocol V comparing focal laser to prompt aflibercept to observation among eyes with center-involved DME without visual loss; the TIME-IIb trial evaluating subcutaneous AKB-9778 for treatment of nonproliferative diabetic retinopathy; and additional results of early phase trials evaluating gene therapy for wet AMD."

—Charles C. Wykoff, MD, PhD, Chief Medical Editor

2019 is poised to be an active year for new treatments for age-related macular degeneration or diabetic macular edema, and in many cases both. Our annual listing of investigative chemical and biologic agents (and one light therapy) in Phase I trials and beyond numbers at least 20 with notable milestones ahead.

Novartis anticipates Food and Drug Administration approval for brolucizumab, which many pharmaceutical analysts say could become one of the leading drugs for neovascular AMD and DME. Regeneron anticipates two significant events this year for Eylea (aflibercept): launch of the prefilled syringe; and FDA action to add diabetic retinopathy as an indication.

A comprehensive list of drugs in development for AMD and DME is almost impossible to fit on one page (*Table, page 32*). Four agents have been added to the list, and four were removed. Abicipar pegol (Allergan) was omitted last year because no milestones were anticipated (turns out top-line Phase III data came out). Other new entrants are elamipretide (Stealth BioTherapeutics); KSI-301 (Kodiak Sciences); THR-317 (Oxurion); and Valeda Light Delivery System (LumiThera). Deleted are nesvacumab (Regeneron), RG7417 (lampalizumab, Roche/Genentech), OHR (Ohr pharmaceuticals) and X-82 (vorolanib, Tyrogenex). Their development programs were terminated. Two name changes occurred: Faricimab (Roche/Genentech) was listed as RG7716; and Luminate (Allegro Ophthalmics) now has the generic name risuteganib.

This list was compiled with the help of Editorial Board member Emmett T. Cunningham, MD, PhD, and is based on presentations at the American Academy of Ophthalmology Retina Subspecialty Day, American Society of Retina Specialists 2018, Retina Society and Ophthalmology Innovation Summit, as well as our own research and verification. A report on gene therapies will appear later in the year.

Abicipar pegol (Allergan/Molecular Partners)

When SEQUOIA and CEDAR trial results of abicipar for nAMD came out, some clinicians expressed concerns about reported relatively high rates of inflammation. The website *Pharmaceutical Technology* reported that three investigators

noted the trials "may have" had cases of hemorrhagic vasculitis, but specifics of the cases were difficult to ascertain. Rates of intraocular inflammation were 15.7 percent and 15.3 percent in the eight- and 12-week abicipar groups, respectively, and 0.6 percent in the Lucentis (ranibizumab, Roche/Genentech) arm.

Both trials showed similar efficacy of abicipar after six or eight injections vs. 13 for Lucentis after a year, with similar adverse event profiles among the three treatment arms (abicipar every eight and 12 weeks, Lucentis every four weeks). The percentage of patients with stable vision ranged between 91 and 96 percent across all three treatment arms in both studies. Allergan said it would use a modified formulation for the MAPLE trial. Allergan expects to file a biologics license application with the FDA in the first half of this year.

AKB-9778 (Aerpio Pharmaceuticals)

Investigators in January completed patient dosing in the Phase IIb TIME trial of AKB-9778 for severe nonproliferative diabetic retinopathy. Administered via subcutaneous injection, AKB-9778 binds to and inhibits vascular endothelial protein tyrosine phosphatase, which negatively regulates Tie2. The TIME Phase Ia study showed improvement in diabetic retinopathy and kidney function. Top-line Phase IIb results are expected in March.

APL-2 (Apellis Pharmaceuticals)

APL-2 proves that drug development doesn't always follow a linear path. In June 2018, the FDA granted fast-track designation to APL-2 for treatment of geographic atrophy. APL-2 is a novel inhibitor of complement factor C3 administered intravitreally. One month after initiating the Phase III DERBY and OAKS trials, Apellis voluntarily suspended them because a few patients had noninfectious inflammation from a single manufacturing lot of the product. In the Phase II FILLY trial, one case of noninfectious inflammation was reported in more than 1,500 patients dosed. Apellis says it will restart the trials in the second quarter and expects full enrollment by early 2020.

Brolucizumab (Novartis)

Novartis last year announced two-year results from the Phase III HAWK and HARRIER trials that reaffirmed positive one-year findings. This small-molecule, single-chain antibody fragment clears more rapidly from the circulatory system than larger-molecule agents. In a head-to-head study of nAMD patients, HAWK and HARRIER findings demonstrated that fewer patients had intraretinal fluid (IRF) and/or subretinal fluid (SRF) with brolucizumab 6 mg vs. Eylea at 96 weeks (24 vs. 37 percent in HAWK [p=0.0001], and 24 vs. 39 percent, respectively, in HARRIER [p<0.0001]).

Other key findings: absolute reductions in CST from baseline were -175 µm for brolucizumab 6 mg vs. -149 µm for Eylea (HAWK, p=0.0057) and -198 µm vs. -155 µm, respectively (HARRIER, p<0.0001). Eighty-two percent of brolucizumab 6 mg patients who successfully completed one year on 12-week dosing in HAWK and 75 percent in HARRIER were still on 12-week dosing in the second year. Novartis says it expects FDA approval for nAMD in 2019.

DE-122 (carotuximab, Santen)

Top-line Phase I/II results of DE-122 for refractory wet AMD presented last year at the Annual Angiogenesis, Exudation, and Degeneration symposium reported no serious adverse events and suggested bioactivity, as measured by mean change in CST. The Phase IIa trial is evaluating intravitreal injections in combination with Lucentis vs. Lucentis monotherapy, with results expected in the first half of 2019. Carotuximab is a novel antibody to endoglin, a protein overexpressed on endothelium essential for angiogenesis and upregulated by anti-VEGF.

Elemipretide (Stealth BioTherapeutics)

The FDA in December 2018 granted Stealth BioTherapeutics fast-track

Expert commentary

"I'm looking forward to having brolucizumab in our clinics as the data are extremely impressive, particularly given the unmet need seen in busy clinical practices. While I generally tend to place my faith exclusively in prespecified, alpha-protected, primary endpoints, the uniform directionality of the secondary endpoint data and absent safety signals in these trials is encouraging."

—Jonathan L. Prenner, MD

"I would be paying attention to the ongoing Phase III trial of APL-2. My interest stems from several aspects, including the fact that we still do not have any treatment for geographic atrophy, that other drugs have failed previously, any safety related signals and potentially adding to the intravitreal injection treatment burden if it's shown to be efficacious."

—Judy E. Kim, MD

Table. Age-related macular degeneration, diabetic macular edema pipeline

Drug name (manufacturer)	Description/active agent	Indication	Status
Abicipar pegol (Allergan/ Molecular Partners)	DARPin therapy	Neovascular age-related macular degeneration	Top-line Phase III data summer 2018. Reformulated for MAPLE trial. Biologics License Application expected 1H 2019.
AKB-9778 (Aerpio Therapeutics)	Small-molecule Tie-2 Activator	Moderate/severe nonproliferative diabetic retinopathy	Data from TIME Phase IIb trial due 2Q 2019.
AKST4290 (formerly ALK4290) (Alkahest Inc.)	Oral CCR3 inhibitor blocks eotaxin	nAMD	Top-line data from two Phase II trials Dec. 2018.
APL-2 (Apellis)	Complement C3 inhibitor	Dry AMD/geographic atrophy	Enrollment in Phase III trials halted October 2018; enrollment to resume in 2019.
Brolucizumab (Novartis)	RTH258 humanized monoclonal antibody fragment (scFv)	nAMD	Two-year Phase III results October 2018. FDA approval expected 2019.
DE-122 (Santen/TRACON Pharmaceuticals)	Carotuximab endoglin antibody	nAMD	Positive Phase I/II results February 2018. Phase IIa results expected 1H 2019.
Eylea (Regeneron Pharmaceuticals)	Aflibercept	Diabetic retinopathy	One-year Phase III PANORAMA trial results for nonproliferative DR due in 2019. FDA target action date May 2019.
Eylea pre-filled syringe (Regeneron Pharmaceuticals)	Aflibercept	All approved indications	Resubmission of prior-approval supplementation expected in early 2019; launch expected 2019.
Faricimab (Roche/Genentech)	Anti-VEGF + anti-Ang-2 bispecific antibody	nAMD, diabetic macular edema	Positive Phase II STAIRWAY (nAMD) data reported Oct. 2018. Phase III YOSEMITE, RHINE (DME) enrolling.
GB-102 (Graybug Vision)	Sunitinib malate (pan VEGFR antagonist)	nAMD	Top-line Phase I ADAGIO data presented January. Phase II PRELUDE trial to start 2H 2019.
ICON-1 (Iconic Therapeutics)	Anti-tissue factor fusion protein	AMD	Phase II trials reported in 2018. Investigational new drug enabling studies expected in 2019.
KSI-301 (Kodiak Sciences)	Antibody biopolymer conjugate	nAMD, DME, retinal vein occlusion	Phase Ia single ascending-dose trial (DME) completed Dec. 2018; Phase Ib study (nAMD, DME, RVO) recruiting.
Risuteganib (Allegro Ophthalmics)	Luminate broad-spectrum anti-integrin peptide	DME, dry AMD	Phase III (DME) to start 2019. Top-line Phase IIa (dry AMD) trial due mid-2019.
OPT-302 (Ophthea)	"Trap" mechanism targets VEGF-C and VEGF-D	nAMD	Positive Phase I/IIa trial in combination with ranibizumab Oct. 2018; Phase IIb readout due early 2020.
PAN-90806 (PanOptica)	Topical selective anti-VEGFR	nAMD, DME, RVO	Data from monotherapy trial due mid-2019.
Port Delivery System with ranibizumab (Roche/Genentech)	Refillable eye implant	nAMD	Positive Phase II Ladder trial Oct. 2018; Phase III Archway trial initiated September 2018.
Elamipretide (Stealth BioTherapeutics)	Daily subcutaneous injections	Dry AMD with GA	FDA fast-track designation December 2018. Phase IIb trial to launch in early 2019.
THR-317 (Oxurion)	Anti-placental growth factor antibody	DME, macular telangiectasia type 1	Positive Phase I/IIa top-line data Oct. 2018. Phase II trials of combination therapy with ranibizumab (DME), monotherapy (MacTel1) enrolling.
Valeda Light Delivery System (LumiThera)	Light delivery system using photobiomodulation	Dry AMD	EU CE mark in 2018. Positive 12-month LIGHTSITE I trial results May 2018. U.S. companion study in development.
Zimura (Ophthotech Corporation)	Avacincaptag pegol complement factor C5 inhibitor	nAMD	Positive six-month safety results from Phase IIa trial of combination therapy with ranibizumab Nov. 2018.

designation for elamipretide for treatment of dry AMD with geographic atrophy via daily subcutaneous injection over 24 weeks. A Phase IIb trial is scheduled to begin early this year. The FDA also granted fast-track designation to elamipretide for treatment of primary mitochondrial myopathy, Barth syndrome and Leber's hereditary optic neuropathy.

Eylea (aflibercept, Regeneron)

Last year, the FDA approved a modified 12-week dosing schedule for Eylea in patients with nAMD. This year, Regeneron expects to launch the Eylea

prefilled syringe.

Regeneron also reported at AAO 2018 that the Phase III PANORAMA trial in patients with moderately severe and severe non-proliferative diabetic retinopathy met its one-year endpoint: 80 percent and 65 percent of patients on every eight- and 16 week dosing (after an initial monthly dosing period), respectively, had a two-step or greater improvement on the Diabetic Retinopathy Severity Scale vs. 15 percent receiving sham injection ($p<0.0001$). The FDA has assigned an action date in May for this indication.

A separate ongoing trial by the Diabetic Retinopathy Clinical Research Network, known as Protocol W, is evaluating Eylea for treatment of NPDR in patients without DME. At the J.P. Morgan Healthcare Conference in January, Regeneron disclosed that it expects to enter clinical trials this year with a high-dose formulation of Eylea.

Faricimab (Roche/Genentech)

This novel small-molecule, bispecific antibody for nAMD was the subject of positive results from the Phase II STAIRWAY trial reported at AAO 2018. The trial evaluated outcomes of faricimab 6 mg dosed every 16 or 12 weeks after four loading doses and Lucentis 0.5 mg every four weeks. At 24 weeks, after the loading doses, those in the 16-week dosing group had a mean improvement of 11.4 chart letters vs. 10.1 letters for the 12-week group and 9.6 letters in the Lucentis group. Formerly known as RG7716, faricimab simultaneously binds to and neutralizes both angiopoietin-2 and vascular endothelial growth factor A. The Phase III RHINE and YOSEMITE studies in DME, and the PHASE III STAIRWAY study in nAMD are expected to start enrollment this year.

GB-102 (sunitinib, Graybug Vision)

GB-102 is an injectable formulation of sunitinib, a tyrosine kinase inhibitor that blocks multiple VEGFR pathways. The goal is to reduce injection burden to once or twice a year. Results of the ADAGIO Phase I/IIa study of GB-102 in patients with wet AMD, which David S. Boyer, MD, reported at the 2019 Hawaiian Eye & Retina meeting, showed GB-102 was well-tolerated with no dose-limiting toxicities, drug-related serious adverse events or inflammation, and 88 percent and 68 percent of patients were maintained only on a single dose of GB-102 at three and six months, respectively. The Phase IIb PRELUDE trial is expected to begin enrollment in the first half of this year.

ICON-1 (Iconic Therapeutics)

This first-generation tissue factor antagonist demonstrated target engagement, biologic activity and the ability to impact important clinical endpoints in the Phase II EMERGE trial, reports Iconic Therapeutics. A second Phase II trial, known as DECO (for Dose Exploration and Continuation Option), started enrollment in May 2018, recruiting patients with choroidal neovascularization secondary to AMD. Iconic last year initiated a Phase II trial of intravitreal ICON-1 both in combination with Eylea and after Eylea in patients with nAMD.

KSI-301 (Kodiak Sciences)

KSI-301 is a completely new anti-VEGF antibody biopolymer conjugate. Twelve-week data from a Phase Ia single ascending-dose study showed a clinical response in eight of nine patients with severe DME. Pooled data across three dosing levels showed median improvements of 9 letters in best-corrected visual acuity and 121 µm in central retinal thickness. The 5-mg dose will be the subject of pivotal studies in severe DME. A Phase II comparison study with Eylea is on track to begin enrollment in the second quarter this year.

OPT-302 (Opthea)

This intravitreal agent inhibits vascular endothelial growth factors C and D. A Phase I/IIa trial is evaluating OPT-302 in combination with Lucentis for nAMD. At 12 weeks, treatment-naïve patients ($n=18$) had a more robust improvement in BCVA (+10.8 vs.

Expert commentary

"In 2019 we will see the early results of GB-102, an intravitreal depot formulation of sunitinib malate, a receptor tyrosine kinase inhibitor, that will show long-term (six-month) treatment effect in eyes with wet macular degeneration. This drug could result in a paradigm shift, if approved, in our management of wet macular degeneration, diabetes and retinal vascular occlusions."

—David S. Boyer, MD

"KSI-301 is a novel anti-VEGF antibody biopolymer conjugate (ABC) designed to improve intraocular durability. Antibody biopolymer conjugates built using a unique phosphoryl-choline biopolymer have the potential to improve treatment outcomes by optimizing intraocular half-life, retinal tissue bioavailability, potency and molar dose of intravitreally delivered biologics."

— Diana V. Do, MD

Expert commentary

"2019 will likely bring us a longer acting anti-VEGF agent for neovascular AMD with the potential FDA approval of brolucizumab, and it will also be a year to provide more clinical trial data on emerging long-acting drug delivery in the form of injectable therapeutics, devices and gene therapy."

—Carl Regillo, MD

"Here is a list of the most exciting classes of drugs in order of anticipated approval: next-generation anti-VEGF; combination; gene therapy. VEGF-A is a well validated target which will be more efficiently suppressed by the next generation of drugs. Combination agents will aim to have an additive effect. Finally, the gene therapy agents will attempt to provide greater efficacy and durability of treatment."

—Pravin U. Dugel, MD

+4.9 letters) and CST (–119 µm vs. –54 µm) than prior-treatment patients (n=20). The Phase Ib dose-escalation DME study evaluated OPT-302 in combination with Eylea, and found a dose-related response to gains in visual acuity and retinal inflammation.

PAN-90806 (PanOptica)

The company describes this as a topical, selective, small-molecule anti-VEGF agent. Last May PanOptica initiated a Phase I/II dose-ranging trial of 60 patients with nAMD. Trial subjects will use the drop daily for three months. The study is due for completion in the first half of 2019.

Port Delivery System with ranibizumab (Roche/Genentech)

This refillable implant, known as PDS, serves as a micro-reservoir of sorts. It is surgically placed in the pars plana to provide a continuous release of ranibizumab. The aim is to go six months between refills. Top line results in 2018 showed that 80 percent of patients in the 100-mg/ml high-dose group went six months between refills and achieved similar visual outcomes as the ranibizumab 0.5-mg group dosed every four weeks. Based on those results, Genentech initiated the Phase III Archway trial in September 2018 to evaluate the PDS 100 mg/mL concentration in patients with nAMD on a fixed dosing interval of 24 weeks compared to monthly ranibizumab 0.5 mg. The estimated completion date of the trial is May 2022.

Risuteganib (Luminate, Allegro Ophthalmics)

Allegro adopted the generic drug name risuteganib for Luminate and anticipates starting a Phase III DME trial in the first half of 2019. Risuteganib targets all four oxidative stress pathways in DME: increased vascular permeability; angiogenesis; inflammation and cell death; and neurodegeneration. The Phase IIb DEL MAR trial demonstrated that risuteganib monotherapy and sequential therapy were non-inferior to bevacizumab (Avastin, Roche/Genentech), being most effective in patients with persistent active DME and a history of anti-VEGF treatments. The Phase III trial will adhere closely to what worked well in the Phase IIb DEL MAR trial. Top-line Phase IIa results in dry AMD are also due mid-year.

THR-317-001 (Oxurion)

Oxurion is pursuing three clinical programs in DME with its lead candidate, THR-317-001, which utilizes placental growth factor. Positive top-line 90- and 150-day data on safety and clinical activity from a Phase I/IIa trial in DME were reported last year. Also enrolling are Phase II trials in combination with Lucentis for DME and monotherapy for macular telangiectasia. Oxurion has two other programs targeting novel pathways in DME: THR-149, a plasma kallikrein inhibitor; and THR-687, an integrin antagonist.

Valeda Light Delivery System (LumiThera)

Valeda employs a process called photobiomodulation to apply a series of light-based treatments to retinal cells, with the aim of improving energy production and addressing inflammation, ischemia and metabolic dysfunction. The system was granted CE (European conformity) in June 2018. Updated results from LIGHTSITE I showed 50 percent of treated eyes (n=15 patients) achieved >5-letter gain a month after treatment, with retreatment needed at six-month intervals. LumiThera has ongoing multicenter studies in Europe and is developing a companion study in the United States.

Zimura (avacincaptad pegol, Ophthotech)

Despite positive Phase IIa trial results of this complement factor C5 inhibitor in combination with Lucentis for nAMD, Ophthotech Chief Medical Officer Kourous Rezaei, MD, said the company would shift focus to other Zimura programs in geographic atrophy secondary to dry AMD and autosomal recessive Stargardt's disease.

Why you need an online brand

Crafting your own unique identity is the first step in embracing the potential of social media.

Welcome to the first "Social Media Specialist" column. My aim is to discuss online strategies and social media platforms relevant to retina specialists. Each column will review key aspects of the changing online media landscape and how you can successfully navigate its contemptuous currents and incorporate them into practice building and online reputation management. This column is not meant to be dogmatic: These are my considerations for online media specifically for physicians.

As any of you who have talked about these topics with me know, I appreciate the opportunity to delve into new territories, and social media is one of these novel terrains. Although the medical, ophthalmic and vitreoretinal spaces can be more conservative in these regards, we are now beyond a tipping point where social media is pervasive and of priority.

Branding can unlock full potential

Let's start with the basis for all online presence and social media awareness: brand. Social media is primarily a reflection of branding. For ophthalmologists and retina specialists, branding is the key to unlock the full potential of social media.

What is a brand? Simply defined, it's an "identifying mark". With origins in the branding of livestock, a brand signifies a specific, non-generic mark. In livestock it was used to attribute specific ownership, but in our context we can think of a brand as a non-generic "brand name" similar to the proprietary name of a branded drug. At the very least, when we extend the definition of brand to this point, we can use it to imply some description of the source or qualities of a product or service.

Transforming brand into our space

Next, we transform this straightforward definition of brand into the medical and vitreoretinal space. In this regard, I have come to define a brand as the intangible sum of a service or product's attributes. As a retina specialist, you deliver care.

Your brand needs to create a specific perception about the qualities of this non-generic service or product. Remember, your practice is specific to you and your partners.

Why branding is essential

This is essential because there is no successful path to physician or practice visibility via social media without brand definition and awareness. The brand is the basis of the relationship formed between patient, client or consumer and the product or service (i.e., health care) consumed. You and your practice need to have a defined brand.

Your practice's brand informs everything you do. From the training of staff to organizational culture to emphasis on preferred practice protocols, everything must be aligned with your branding message. If you don't have a brand, then you need to assess and reflect on what is most important to you and your practice.

Using brand as promotional tool

Luckily, in most medical contexts, delivering the best possible care and working toward the most favorable patient outcomes is common ground you can draw on in defining your brand. If you get nothing else from this first column but to crystalize the brand you value for yourself and your practice, this will pay multiple dividends.

From this discussion on brand, we can now move on to other aspects of online media presence and how you can maneuver in this space to promote a physician or practice. In my next column, I'll review the major social-media platforms and online physician ratings sites.

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2019 updates, changes and trends

Some of the coding changes are minor, others not so. Here's a rundown.

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The new year has come and with it several coding changes and updates. Some of the changes are minor while others are more significant. Here, we'll touch on changes in Current Procedural Terminology (CPT) codes, reimbursement rates, a few administrative matters and some miscellaneous items like utilization for various services, along with an important update to the Merit-based Incentive Payment System (MIPS).

Physician Fee Schedule changes

The Centers for Medicare and Medicaid Services published the 2019 Medicare Physician Fee schedule in November.[1] The conversion factor remained relatively flat, increasing slightly from 35.9996 to 36.0391. Conversely, Table 1 lists several noteworthy changes in reimbursement from 2018 to 2019. The largest changes in reimbursement occurred in the test category, which includes ultrasounds as well as imaging.

The 2019 rates for surgical procedures, including intravitreal injections, vitrectomy procedures and lasers, remained within 1 percent of 2018 rates. The exception is a 19 percent reduction to CPT 67515, "Injection of medication or other substance into Tenon's capsule."[2] Office visit codes commonly used by retina specialists, including 99205, 99215, 99204, 99214, 92004 and 92014, also remained within 1 percent of the 2018 rates.

Code changes

Electroretinograpy testing has undergone numerous CPT changes. The longstanding ERG code, 92275, "Electroretinography with interpretation and report," was deleted in 2019. In its place, CPT added three new codes:

- ***92273*** —Electroretinography (ERG), with interpretation and report; full field (i.e., ffERG, flash ERG, Ganzfeld ERG).
- ***92274***—ERG with interpretation and report; multifocal (mfERG).
- ***0509T***—ERG with interpretation and report, pattern (PERG).

CPT added new instructions to assist with code selection for the different ERGs. The guidance requires that the ERG testing method must match the techniques listed in each code. If not, the unlisted code is to be used. It states:

> *ERG is used to evaluate function of the retina and optic nerve of the eye, including photoreceptors and ganglion cells. A number of techniques that target different areas of the eye, including full field (flash and flicker, 92273) for a global response of photoreceptors in multiple separate locations in the retina, including the macula, and pattern (0509T) for retinal ganglion cells are used. Multiple additional terms and techniques are used to describe various types of ERG. If the technique used is not specifically named in the code descriptions for 92273, 92274, 0509T, use the unlisted procedure code 92499.*[2]

The rates for the three new codes, 92273, 92274 and 0509T, are $136, $92 and $81, respectively (0509T is a Category III code,

Table 1. Reimbursement changes for 2019

CPT	Description	Change 2018 to 2019 (%)
76510	B-Scan and quantitative A-Scan	-19
76512	B-Scan	-19
76511	Quantitative A-scan	-17
92250	Fundus photography	-12
92227	Remote imaging to detect retinal disease (telemedicine)	-5
92240	ICG angiography	-2
92134	OCT Retina	-2
92020	Gonioscopy	+3
92235	Fluorescein angiography	+6

which means reimbursement and coverage is at the payer's discretion). These rates are less than the 2018 rate of $153 for 92275.

In October 2018, the Food and Drug Administration approved the new fluocinolone acetonide implant (YUTIQ, EyePoint Pharmaceuticals), for treatment of chronic non-infectious uveitis affecting the posterior segment.[3] Use supply code J7313 "Injection of fluocinolone acetonide, intravitreal implant, 0.01 mg" with 18 units when submitting a claim.

Administrative changes

Several other areas changed as well. First, the annual deductible for Medicare Part B increased $2 to $185.[4] Second, CMS is reversing the Change Request (CR) 10318 to the National Coverage Determination (NCD) 80.11 Vitrectomy, implemented in October 2017,[5] that caused erroneous vitrectomy denials. CR 10859, released September 2018 and revised in November, published that all ICD-10 codes removed in 2017 are reinstated retroactively to before CR 10318 was published.[6]

The CMS Quality Payment Program (QPP) made several changes in 2019. The most noteworthy is an increase in the performance threshold to avoid the penalty for physicians and/or physician groups participating in MIPS. For 2019, the threshold to avoid a penalty in 2021 increased from 15 points in 2018 to 30 points in 2019.[7] The range for payment adjustments in 2021 based on 2019 participation increases to +/- 7 percent.[8]

Utilization changes

Some noteworthy changes in select services that ophthalmologists provide to Medicare beneficiaries occurred between 2016 and 2017. While Medicare does not report "Retina only" data, retina specialists provide many of the services listed in Table 2, which shows the percentage of change in volume from 2016 to 2017.

It's important to note that the large decrease in volume for fluorescein (92235) and indocyanine green (92240) angiography resulted from both codes being modified from unilateral to bilateral in 2017. Prior to 2017, the two codes reimbursed for each eye.

Table 2. Utilization changes between 2016, 2017

CPT	Description	Utilization Change (%)
67028	Intravitreal injection	+6
67145	Laser prophylaxis	+11
67210	Focal laser	-5
67228	Panretinal photocoagulation laser	-9
92134	Optical coherence tomography retina	+5
92225/6	Extended ophthalmoscopy	+16
92235	Fluorescein angiography	-53
92240	Indocyanine green angiography	-90
92275	Electroretinogram	+12
99204	Evaluation/management (E/M) new patient	+18
99214	E/M established patient	+7
99205	E/M new patient	+5
99215	E/M established patient	+4

Bottom line

For 2019, there are several important changes in reimbursement for selected codes, including ERG testing. Monitor payment for vitrectomy procedures to ensure Medicare and other payers that follow NCD 80.11 process claims accurately. Finally, MIPS is not going away. In fact the threshold to avoid a penalty in 2021 doubled in 2019.

MIPS is not going away. In fact, the threshold to avoid a penalty in 2021 doubled in 2019.

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

A far reach: PPV in highly myopic eyes

(Continued from page 17)

Alcon products, 23-gauge instruments (or 25-gauge, non-plus) are approximately 1 to 2 mm longer than 25-gauge-plus instruments that have a stiffening sleeve. Longer forceps designed for high-myopia cases are also available (e.g., Dutch Ophthalmic Research Center [DORC] or Synergetics/Bausch + Lomb Retina).

If you get caught in a pinch and need additional reach from standard forceps, remove the cannula after complete removal of the vitreous gel. Otherwise there is a risk of entry-site associated dialysis. As a last resort, the infusion pressure can be lowered to allow partial compression of the globe, but this causes optical distortions that can make fine macular work difficult.

Macular manipulation

A myopic, tessellated fundus can make visualization of membranes and the internal limiting membrane difficult. Adjuncts, including triamcinolone, brilliant blue or indocyanine green, can enhance visualization. Gently instill and remove these adjuncts because the retinal tissue can be very thin. A sudden jet from an injection or an infusion can cause iatrogenic damage or even a retinal break including, macular hole.

Even for patients with a clinical posterior vitreous detachment, there can often be an element of residual vitreous membranes on the posterior pole as well as mid- to peripheral retina. Triamcinolone can be helpful to identify residual vitreous, which can promote growth of epiretinal membranes and/or proliferative vitreoretinopathy.

Initiating ILM peel at the temporal raphe can minimize mechanical damage to the retinal nerve fibers. In cases with schisis, a fovea-sparing ILM peel may be desirable to limit the chance of progression to full-thickness macular hole.[1]

For myopic macular holes with and without retinal detachment, inverted ILM flap technique may facilitate anatomic success. If you have to use an autologous ILM flap, perfluorocarbon may be helpful to stabilize the ILM flap even after fluid-air exchange. Other options include autologous retinal graft[2] and amniotic membrane[3] for refractory macular hole cases.

Bottom line

The next time that a high myope is sitting in your examination chair, don't let that big eye worry you. Use these pearls to formulate the proper preoperative plan and obtain any special instrumentation that may be required in the setting of extreme axial length. Thinking carefully about the goals of surgery and the operative approach in these fragile eyes will minimize iatrogenic complications and maximize success.

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Current and future therapy

(Continued from page 26)

corticosteroid in noninfectious uveitis.

Bottom line

The armamentarium of corticosteroid injections will likely broaden over the next few years as the longer-acting fluocinolone implants (Iluvien, Yutiq) and the novel delivery systems (Xipere) become more widely available. Retina specialists can use steroid injections that we utilize for other conditions and apply that experience to noninfectious uveitis. Consultation with a uveitis specialist can help guide systemic therapy and give insight into using regional corticosteroid injections into care for these patients.

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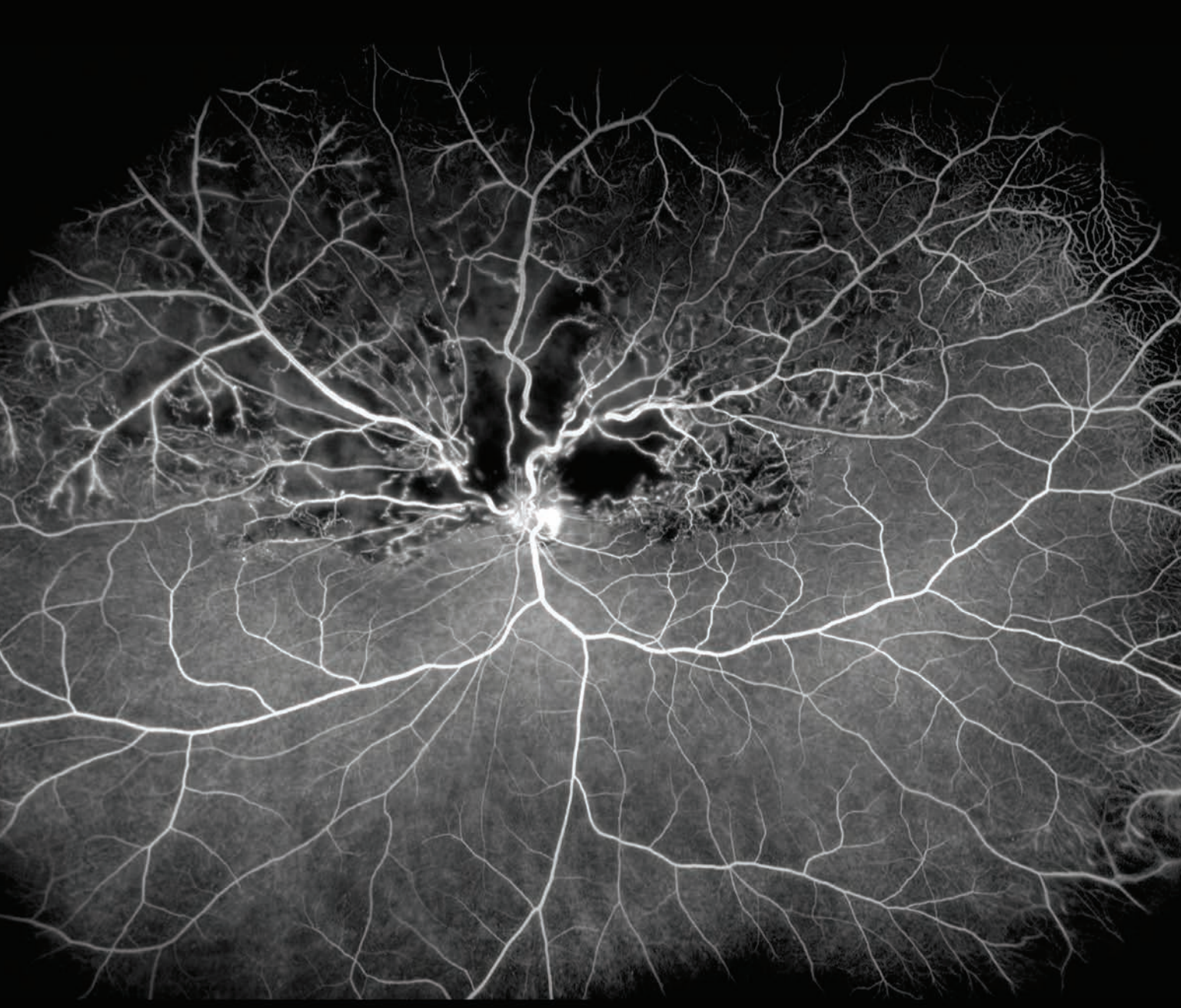

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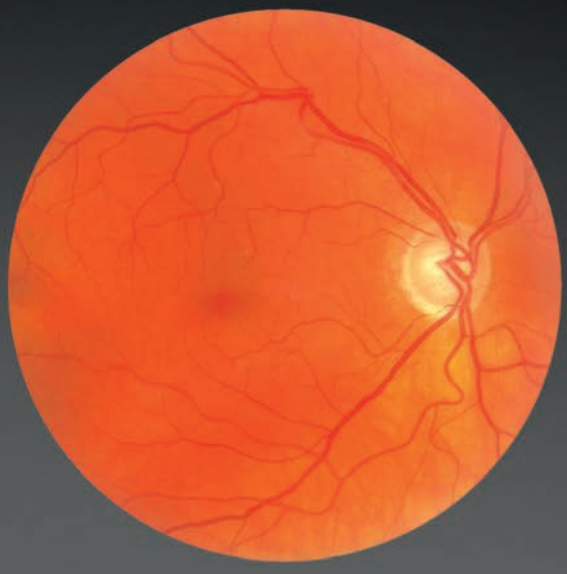

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