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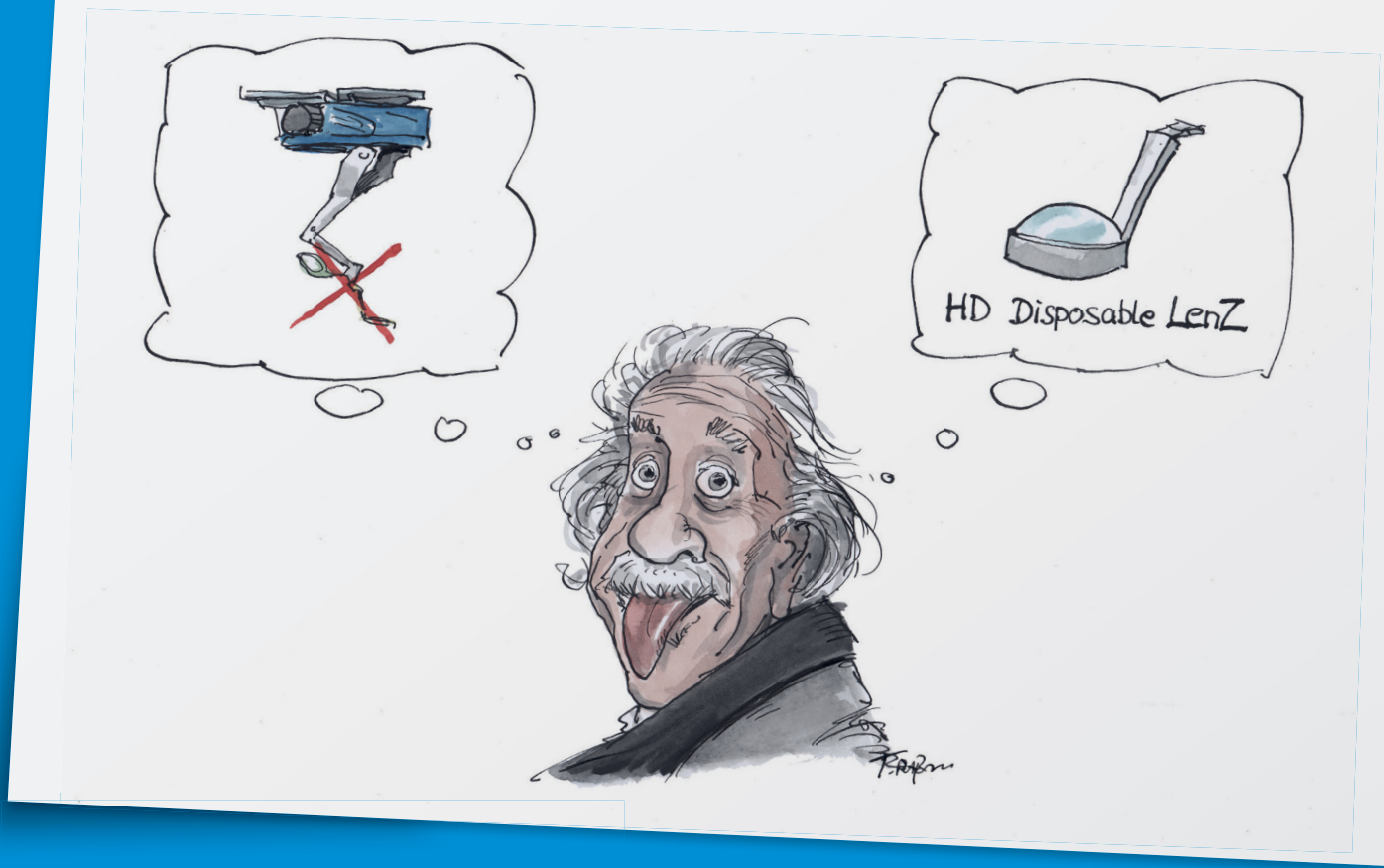

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Caution ahead: Confronting DME

Most atrophic retinal diseases are untreatable, including geographic atrophy. Thankfully, I believe efforts underway will ultimately prove successful in altering this unpleasant reality. Patients are desperate and scared, and our society has a long history of preying on these base human emotions. Too often such patients turn to patient-funded stem-cell research or buy some nonrefundable, useless visual aide like "pinhole glasses."

Diabetic retinopathy is different. Because the attributable blindness is arguably almost completely preventable, the scale of the associated permanent vision loss is a particularly noxious scourge.

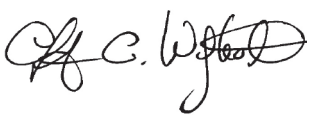
Some studies have indicated that supplemental physician education of DR patients may not have a meaningful impact. Reassuringly, many studies have reported that patients indeed do regard their clinician's recommendations more highly than many other sources of information in our rich, complex, distracting information ecosystem.[1]

As one example, among a population of regular alcohol-consuming cancer patients at diagnosis, simple clinician counseling to quit drinking led to a fivefold greater likelihood of behavior modification. However, such clinician recommendations were remarkably infrequent.[2]

Retina specialists often develop long-term relationships with our patients. Be mindful of both the opportunity and responsibility this affords. Your comments and recommendations can impact patient behaviors, such as cardiovascular risk factor control and choices for managing, or observing, concurrent retinal diseases. We're called to be active participants in our patients' lives instead of being fatalistic observers.

In this issue, Drs. Mustafi Safi and Roger Goldberg report on DRCR Retina Network Protocol V (*page 25*). I think we must remain skeptical about interpreting the results to imply that observation of a clinically relevant amount of center-involved diabetic macular edema is the best course for all patients with visual acuity better than 20/32. No data suggest DME, even without dramatic VA loss, is beneficial for an eye.

Therefore, even though our current therapeutics, which require intravitreal delivery, carry risks and aren't an optimal approach, we must remain vigilant in our goal to prevent needless visual loss. We must be willing and able to re-evaluate our threshold for initiating treatment as individual patient circumstances evolve, new therapeutics emerge and more data is generated. RS



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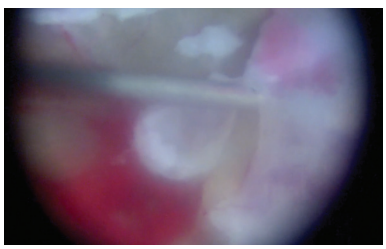
DEPARTMENTS



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What Novartis hopes to learn from its review of Beovu AEs

In response to reports of inflammation and vasculitis in patients who've had intravitreal injections of Beovu (brolucizumab), Novartis has initiated a review of the reports that involves a multilayered approach, including the customary postmarketing review, the company announced eight days after the American Society of Retina Specialists sent an update to members alerting them to the adverse events.

"Any time a patient experiences an adverse event it's deeply concerning to us," says Marcia Kayath, MD, PhD, MBA, Novartis global head of medical affairs and chief medical officer, in an interview with *Retina Specialist*. "We completely understand the medical community's concerns; so patient safety is our first priority. We are committed to providing clarity of these events as soon as possible so the outcomes are given to the retina community."

Dr. Kayath adds that the reported incidence of the adverse events is within the rates on the package insert, which reports a 4 percent rate of intraocular inflammation and retinal hemorrhage and a 1 percent rate of retinal artery occlusion. "We'll continue to monitor the safety of Beovu," she says. "We are committed to sharing the outcomes of the investigation as soon as it's completed, and we stand by the safety and efficacy of Beovu."

In its update, ASRS acknowledged that Beovu is contraindicated in patients with an active inflammation, noting that some cases were observed in patients who had residual inflammation after an earlier anti-VEGF injection. The update urges retina specialists to defer an injection if any "concerning signs" of inflammation are present.

"I am being very judicious about its use until further information about the prevalence and best treatment from these potential adverse events are known better," says Elliott Sohn, MD, at the University of Iowa, one of the first retina specialists to tweet about Beovu-linked inflammation from the Macula Society February 19 to 22 in San Diego, where reports of the adverse events first emerged.

On February 23, the ASRS posted its update to members confirming an unspecified number of cases of mild to moderate intraocular inflammation and 14 cases of vasculitis, 11 of which have been designated as occlusive retinal vasculitis by the reporting providers. At the time, Novartis estimated 46,000 injections had been administered in the United States since Beovu received Food and Drug Administration approval in October 2019. As of Novartis' update, dated March 2, that number had jumped to more than 57,000.

Novartis headquarters in Basel, Switzerland.

Novartis' safety review involves three levels: gathering clinical data from physicians reporting events; using the data monitoring committee (DMC), a standing group that evaluates postmarketing and clinical trial data; and using an external safety review committee (SRC) to further investigate the cases.

"What we are hoping to learn, first

IN BRIEF

Ribomic injected the first U.S. patient in the Phase II trial of **RBM-007** for the treatment of exudative age-related macular degeneration. RBM-007 is an oligonucleotide-based aptamer with anti-FGF2 (fibroblast growth factor 2) activity.

ProQR Therapeutics received a Rare Pediatric Disease designation from the Food and Drug Administration for **QR-421a** for retinitis pigmentosa. The agent is a first-in-class, investigational, RNA-based oligonucleotide designed to target mutations in exon 13 of the USH2A gene.

The Phase III PANORAMA trial evaluating **Eylea** (aflibercept, **Regeneron Pharmaceuticals**) for moderately severe to severe nonproliferative diabetic retinopathy reported the treatment arm had a 75 percent reduced likelihood of developing a vision-threatening complication or center-involving diabetic macular edema vs. sham.

Phase III results of the PEACHTREE trial of **Xipere** (triamcinolone acetonide suprachoroidal injectable suspension, **Bausch + Lomb/Clearside Biomedical**) demonstrated clinically significant improvement in vision in individuals with noninfectious uveitis vs. controls. No serious adverse events were reported.

of all, is the clinical history of these patients: What are the details of the event, concurrent diseases and any patterns," Dr. Kayath says. The review involves collecting clinical images from the providers and classifying them. "Doing a thorough review, we would think that this could allow us to clarify a position, identify patterns and a root cause and lead to potential guidelines for retina specialists," Dr. Kayath says.

With Allergan's reformulation of abicipar-pegol after reportedly high inflammation rates still fresh in retina specialists' minds, Dr. Kayath acknowledges that the Beovu lots used are a consideration in the review. "With the safety surveillance program we are evaluating all aspects of the reported cases, and while we don't have a reason to suspect that formulation is a cause, we are conducting a review of lots and batches as part of our surveillance program," she says.

Novartis has set no time frame for completing the review, but Dr. Kayath says the company will share the findings with the retina community when it's completed.

Three ways to report Beovu adverse events

- The American Society of Retina Specialists suggests retina specialists report adverse events related to Beovu on the ASRS website (www.asrs.org/clinical/adverse-events-reporting).
- Novartis also asks physicians to report AEs at www.report.novartis.com or call 1-888-669-6682 Monday through Friday from 8:30 a.m. to 5 p.m. Eastern Time.
- Retina specialists may also report AEs to the Food and Drug Administration MedWatch program at www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.

How ophthalmologists in Hong Kong deal with COVID-19 outbreak

With the coronavirus spreading in the United States, ophthalmologists here may learn a few things from colleagues in Hong Kong who've already dealt with the outbreak there.

A group of ophthalmologists from the region reported on infection control measures they implemented as coronavirus (COVID-19) spread.[1] They adopted controls on three levels:

• ***Administrative,*** such as reducing patient attendance in the office by rescheduling appointments or prescription refills. This included identifying vulnerable patients and encouraging them to postpone appointments for 14 days, avoiding procedures that generate micro-aerosol particles such as noncontact tonometry, suspending elective procedures and training staff in infection-control practices.

• ***Environmental controls,*** such as reducing droplet transmission, including protective shields on slit lamps, frequent disinfection of equipment, giving all staff eye protection, and directing staff to take their own temperatures before work and promptly report any symptoms.

• ***Promoting use of personal protective measures***, including universal masking and hand hygiene.

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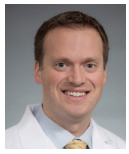
A Coats of many colors

A case of unilateral xanthocoria with distinct central subretinal mass.
By John Davis, MD, Debarshi Mustafi, MD, PhD, and Andrew Stacey, MD


John Davis, MD


Debarshi Mustafi, MD, PhD


Andrew Stacey, MD


Lisa C. Olmos de Koo, MD, MBA

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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. Stacey is an assistant professor of ophthalmology specializing in ocular oncology, Dr. Davis is an ophthalmology resident and Dr. Mustafi a retina fellow.

A 3-year-old boy presented to Seattle Children's Hospital after he'd recently emigrated from Vietnam with his mother. Before leaving Vietnam, a doctor told them the boy had a mass in his left eye requiring medical attention. His ocular history was positive for xanthocoria in the left eye first noticed at age 1. At age 2, the patient was noted to have variable eye crossing.

Records from the most recent ophthalmology visit in Vietnam were limited, but stated that the patient had a normal MRI and no additional treatments to the left eye were recommended. His medical history was unremarkable, and family history was negative for any eye diseases or blindness.

What we found on exam

Full Allen chart visual acuity was 20/20 in the right eye and light perception in the left. Intraocular pressures were soft to palpation and symmetric in both eyes. Pupils were equal and symmetrically reactive without afferent pupillary defect. Extraocular motility was full in each eye. The patient showed a variable esotropia of the left eye. The anterior segment exam was unremarkable in each eye.

The dilated fundus exam was unremarkable in the right eye. In the left eye, the dilated fundus exam demonstrated a large, elevated exudative yellowish lesion extending to encompass the majority of the macula, with a distinct gray central elevation. The macula was surrounded by darkly pigmented retina with numerous small exudates extending along the superior and inferior temporal arcades as well as into the periphery 360 degrees (*Figure 1*).

Workup

B-scan in the clinic demonsirated a lesion approximately 2.5 mm in height with high internal reflectivity. It appeared to be either subretinal or choroidal in location (*Figure 2*). We scheduled an exam under anesthesia (EUA) and obtained handheld optical coherence tomography, which demonstrated retinal exudation overlying a bilobed subretinal mass in the central macula. Minimal subretinal fluid was associated with the mass.

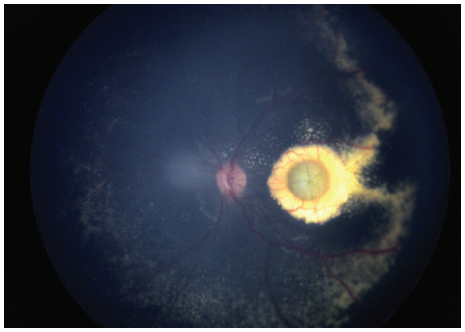

Figure 1. Color fundus photo of the patient's left eye on presentation showing a large elevated exudative yellowish lesion extending to encompass the majority of the macula with a distinct gray central elevation.

The choroid directly adjacent to this mass appeared normal without any engorgement leading up to the highly elevated mass. This suggested that the lesion was subretinal rather than choroidal (*Figure 3*).

Fundus angiography of the left eye using RetCam (Natus Medical) showed early

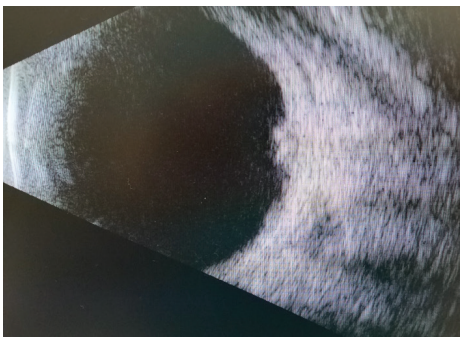

Figure 2. B-scan of left eye on presentation demonstrated a lesion approximately 2.5 mm in height with high internal reflectivity.

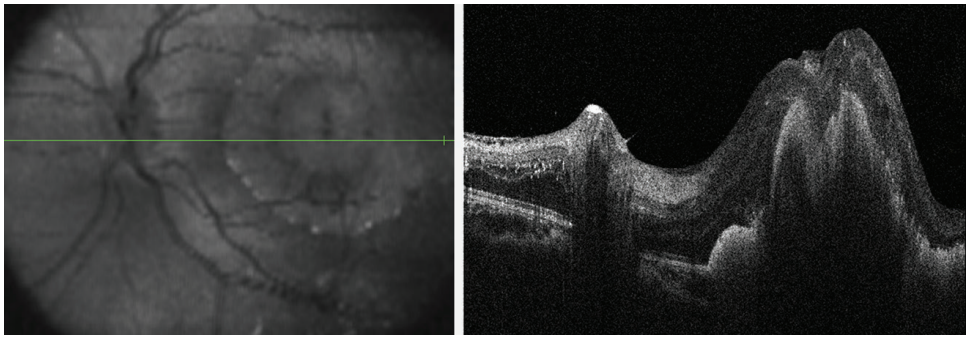

Figure 3. Handheld spectral-domain optical coherence tomography of the left eye during exam under anesthesia showed normal choroid adjacent to the mass but no engorgement, suggesting the lesion was subretinal.

staining in the central macula and in the telangiectatic vessels in the periphery (*Figures 4A, B, page 10*). Late leakage occurred throughout the periphery, particularly in the area of the telangiectatic vessels temporally. The central macula showed only minimal leakage. Late images showed mostly pooling in the central macula (*Figures 4C, D, page 10*). The right eye on late frames was normal. We took color photographs of both eyes to document the lesion.

Diagnosis and management

The initial workup in this young boy with xanthocoria and strabismus was most consistent with Coats disease. The differential diagnosis for Coats disease should include retinoblastoma, toxocariasis, familial exudative vitreoretinopathy and retinopathy of prematurity.

The long history of the disease, including the two-year history of xanthocoria, as well as no significant calcification on B-scan, made retinoblastoma unlikely. However, there was some uncertainty about the nature of the central elevated gray mass. Following EUA and fluorescein angiography demonstrating telangiectatic vessels with late leakage throughout the periphery, we felt confident in the presumed diagnosis of Coats disease, and that the central gray area represented subretinal fibrosis.

In a conversation with the family, we outlined treatment options for the disease. These included observation vs. laser treatment vs. anti-VEGF treatment vs. both laser and injections. After talking with the family, we decided to proceed with peripheral laser therapy but not anti-VEGF therapy.

We examined the patient again under anesthesia. We noted abnormal blood vessels in all peripheral quadrants, with the greatest temporally. We used a laser indirect ophthalmoscope, applying 532-nm laser to the abnormal vessels and exudates temporally and to all quadrants with a total of 1,024 spots, a power of 200 mw and a duration of 100 ms.

Features of Coats disease

Coats disease is a congenital condition characterized by unilateral retinal telangiectasia and exudation that predominantly affects young males. It's named for George Coats, who first described it in 1908.[1]

Jerry Shields, MD, and colleagues later classified the disease with a system to predict visual prognosis by stratifying patients according to the presence of foveal exudation and exudative retinal detachment on presentation.[2] They reported that the absence of foveal exudates at the initial evaluation is cause for a more favorable visual prognosis, while thick foveal exudation usually predicts a worse functional outcome.[2]

Subfoveal nodules in Coats disease

While we were initially surprised to find a subfoveal nodule in our patient, this has

The long history of the disease, including the two-year history of xanthocoria, as well as no significant calcification on B-scan made retinoblastoma unlikely.

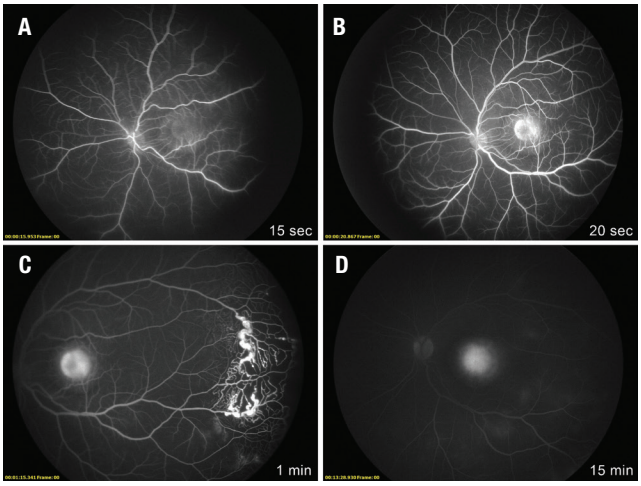

Figure 4. Fluorescein angiography of the left eye showed early hyperfluorescence in the central macula (A, B) and leakage of peripheral telangiectatic vessels (C) with late staining and pooling in the central macula (D).

In deciding on therapeutic options, one should consider the benefits of combined therapy as well as the need for repeated examinations under anesthesia if anti-VEGF therapy is continued.

been well described in the literature and noted by both Drs. Shields and Coats in their descriptions of the disease. Coats described coloration indicating subretinal fibrosis, as in this case, having "in parts a grayish reflex, in others a yellowish-white."[1] Dr. Shields and colleagues found that subretinal fibrosis predicted poor visual outcome (final vision < 20/400). However, they didn't include this in their classification system.[2]

More recent studies have found subretinal fibrosis present in 23 to 28 percent of patients with Coats.[2-6] Alejandro Daruich, MD, and colleagues advocated that this finding should be added to a modified classification system for Coats disease with the addition of subretinal fibrosis to two new subcategories under the original shield classification 2B: 2B1 and 2B2.[7]

Interestingly, additional studies of subretinal fibrosis in Coats disease found a likely vascular component leading to its development. A study by Sally Ong, MD, and colleagues analyzed OCT, fundus photography, fluorescein angiography and histopathology of eyes with Coats disease.[3] This study found intraretinal vessels entering the nodules, leakage on FA and cystoid intraretinal spaces, all of which support the hypothesis that type 3 choroidal neovascular membrane may occur in fibrotic nodules.[3,6]

Bottom line

While we treated this young patient with laser therapy to the abnormal vessels in the retinal periphery, recent studies have shown that submacular fibrosis likely has a vascular component and anti-VEGF therapy may be warranted.

In deciding on therapeutic options, one should consider the benefits of combined therapy as well as the need for repeated examinations under anesthesia if anti-VEGF therapy is continued. We recommend tailoring treatment based on disease severity. Nevertheless, additional research is needed on the safety and efficacy of these treatment options. RS

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Bringing PnR into your practice

Insights for adopting pneumatic retinopexy. By Roxane J. Hillier, MBChB, FRCOphth, MS, David Ta Kim, MD, FRCSC, and Rajeev H. Muni MD, MSc, FRCSC

Pneumatic retinopexy provides functionally superior outcomes to pars plana vitrectomy for a range of rhegmatogenous retinal detachment configurations. The technique offers quick visual rehabilitation and minimal cataract morbidity. It's also highly cost effective.

If you aren't regularly performing pneumatic retinopexy (PnR), you may wish to consider the best way to incorporate it into your established practice. Here, we provide some guidance on how to do that.

Get started with the right patient

For an experienced vitreoretinal surgeon who's proficient at detailed peripheral retinal examination with scleral indentation and indirect laser, optimal outcomes with PnR will follow a short initial learning curve.

Nonetheless, we advise you start out by considering PnR in cases with the highest likelihood of success. From an anatomical perspective, these would be eyes with good pupillary dilation, clear ocular media and with RRD morphology meeting PIVOT trial criteria—that is, all breaks in the detached retina within one clock hour, between 8 and 4 o'clock, with breaks or lattice degeneration in attached retina being permissible.[1] (PIVOT stands for the Pneumatic Retinopexy vs. Vitrectomy for the Management of Primary Rhegmatogenous Retinal Detachment Outcomes Randomized Trial.)

Strict head posturing is imperative

The ideal patient would have excellent comprehension of the need to comply with a strict head-posturing regime, and would be physically able to carry out the instructions.

Additionally, consider practical factors, such as the patient's domestic environment and geography, because they may impact on posturing and follow-up compliance: Does the patient live alone? Is she or he a caregiver? Is there home support? Does the patient live locally?

We can't overemphasize the importance of correct head positioning in ensuring a successful retinal reattachment. Patients' misunderstanding of this are a common cause of delayed reattachment or failure. They must avoid vigorous activity while the gas remains *in situ* to reduce the risk of secondary retinal breaks.

A thorough explanation of the need for posturing, and a detailed description and demonstration of the necessary postoperative steps are crucial. In many cases, written or diagrammatic instructions are helpful. A preprinted sheet for your annotation saves time here.

Recognizing signs of success

In most cases, complete subretinal fluid resolution occurs in the early days following gas injection. However, a delay in the complete resolution of SRF isn't uncommon. It can sometimes linger inferiorly for weeks or even months.

In our experience, this is more often seen in cases of more chronic RRDs, in older patients and in paler fundi, where we suppose that the retinal pigment epithelial pump may be less efficient at SRF clearance. In such cases, the SRF tends to loculate inferiorly, slowly resorbing over time. In these instances, a careful peripheral retinal examination should reveal no open breaks. If the exam does reveal an open break, signs of proliferative vitreoretinopathy developing or SRF increasing, promptly schedule additional surgery.

One way a surgeon can get into trouble with PnR is if she or he waits too long to schedule surgery for a patient who has

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Bios

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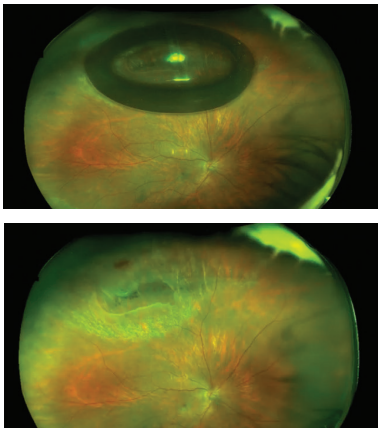

Two widefield imaging views of a superior macula-off retinal detachment after pneumatic retinopexy showing the retina fully attached, the superior break lasered after 48 hours (top) and the gas bubble fully resorbed.

clearly failed the initial procedure. Such cases should be treated within days. A prolonged delay in getting to the operating room can raise the risk of PVR and failure of the subsequent surgical approach.

If a secondary procedure is needed

A secondary surgical procedure on a failed PnR requires some special considerations. If performing a scleral buckle, exercise great caution with trans-scleral drainage of SRF with gas *in situ*. Rotating the eye to gain exposure to the drainage site brings the gas bubble to the location of drainage. In this situation, when the posterior sclerotomy is made and drainage starts, the gas bubble can promote retinal incarceration, retinal tear formation and gas egress from the drainage site. Thus, it's wise to remove all but the smallest gas bubble before drainage.

A further consideration is for phakic patients undergoing subsequent PPV following failed PnR. With gas *in situ*, the patient must adhere to strict face-down posturing until surgery commences. Supine positioning at home and in the preoperative area results in the gas contacting the lens, and can result in lens opacity, thus complicating the case.

A further advantage of face-down positioning during this period is protection of the macular region. In patients having combined PPV/scleral buckle following failed PnR, lens opacity formation is a particular concern because the SB is generally placed first, allowing enough time for a gas-related lens opacity to form. In this situation, it's wise to remove the gas as the first step.

Equipment and facilities

The ability to perform a detailed preoperative peripheral retinal examination with scleral indentation is a prerequisite to success in PnR. Therefore, an examination room equipped with a fully reclining chair and indirect ophthalmoscope is essential. We advocate liberal use of indirect laser pre-, intra- and postoperatively for the treatment of all lattice lesions and retinal breaks in the affected eye. For this reason, indirect laser must be on hand for every clinic visit.

Likewise, for certain cases, cryotherapy is effective and convenient for intraoperative retinopexy and should be available. A potential major advantage of PnR is the accessibility of the technique, free from the need for complex equipment, scrub staff, neurolept analgesia/general anesthesia or, indeed, an operating room. Ready access to a suitably equipped treatment room is highly desirable and allows for swift intervention.

Again, a fully reclining chair or stretcher is preferable, and an operating microscope is useful (although not essential) for performing anterior chamber paracentesis in phakic patients. Postprocedure, it may be helpful to provide an observation area to ensure patient safety and comfort. Such an area would allow for a period of face-down positioning on site to aid in normalization of intraocular pressure and, in some instances, to await for reperfusion of the optic nerve following gas injection.

Nuances of scheduling

Patients undergoing PnR generally need review at 24 to 48 hours post-gas injection. At the first follow-up visit after PnR, patients require more time than the usual retinal clinic consultation if you

Disclosures

The authors have no relevant financial relationships to disclose.

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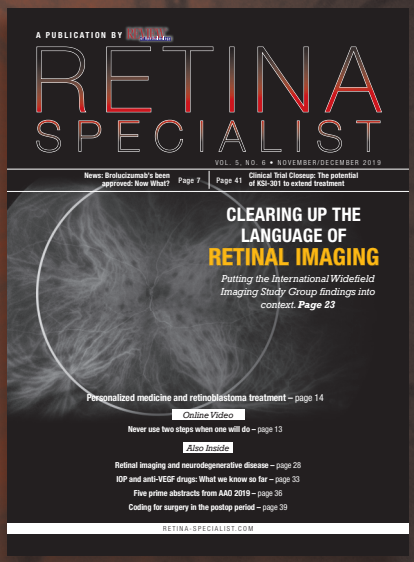

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anticipate indirect laser retinopexy. Furthermore, a second gas injection may occasionally be appropriate, so it's important to schedule these patients with sufficient time. We suggest scheduling them toward the end of the day to help with smooth clinic flow.

Patients who have had pre-PnR cryopexy are more predictable to manage because the responsible break has already been treated. Once retinopexy is complete, PnR patients may be accommodated routinely in the clinic around two weeks later. The vast majority of PnR failures occur in the early weeks, and late redetachments are rare. Therefore, patients may be safely discharged at two to three months post-procedure.

PnR is ideal for fellowship programs that can use a team approach. Fellows at any stage can participate in the procedure and assume more responsibility over time.

Patients who have had pre-PnR cryopexy are more predictable to manage because the responsible break has already been treated.

Tips for fellows

Vitreoretinal fellows should gain proficiency in PnR because it's an important tool in our armamentarium for repairing RRD. The clinical exam is critical, because missed breaks in detached and attached retina lead to procedural failure. Scleral indentation is always necessary and is the only way to identify smaller breaks.

Before starting the exam, inform the patient about possible discomfort. Topical anesthetic should be instilled and the patient reclined for maximum visualization in all quadrants. Indentation can be done over the eyelids or directly on anesthetized conjunctiva using a cotton tip applicator or (ideally) a clean metallic scleral depressor.

During the initial examination, take special notice of landmarks that will help identify the break at a later stage, with gas *in situ* (a distinctive vessel or lattice lesion, for example). For fellows who haven't yet mastered scleral indentation, we advise performing this exam on every retinal patient to gain proficiency.

Explaining the desired postprocedure head positioning to every patient is essential. We suggest giving printed instructions along with a verbal explanation. Patients routinely underestimate the importance of adherence to precise head positioning instructions. They usually comprehend the positioning necessary for breaks at 12, 9 or 3 o'clock pretty well. However, for breaks at around 10:30 and 1:30, where a 45-degree position is warranted, we prefer to ask that patients lie on their side with three pillows rather than have them attempt to sit up with a head tilt at 45 degrees—because they invariably end up more upright than intended.

The most challenging aspect of PnR for the fellow in training is indirect laser. You may administer subconjunctival anesthetic in the vicinity of the anticipated treatment, especially when you're early in the learning curve. Another tip is to irrigate povidone iodine from the conjunctival sac with balanced salt solution after the gas injection to preserve the clarity of the ocular surface for the laser a day or two later. If the ocular surface remains irritated at that stage, BSS or artificial tears may be applied. Laser can be applied either through the gas bubble or through the vitreous, by tilting the head to divert the gas away from the break—but avoid the meniscus. Scleral indentation under the retinal break can help to bring it into view and aid with laser uptake.

Early on, close senior guidance is needed to maximize anatomical success rates. Fellows should communicate with the staff vitreoretinal surgeon at each visit about the evolution of their PnR cases. Such close communication will maintain good outcomes while offering the best learning experience. RS

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Department Editor ***Paul Hahn, MD, PhD***

Pearls for complex diabetic TRD repair

Patience and persistence are key to relieving the tractional forces on the retina.
By Rahul Komati, MD, and Dimitra Skondra, MD, PhD

Taking on a diabetic tractional retinal detachment can be daunting for any vitreoretinal surgeon. But careful preoperative planning and meticulous surgery can achieve good outcomes for these complex cases.

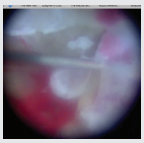
Preoperatively, we like to perform panretinal photocoagulation to the attached retina a few weeks before surgery and routinely inject bevacizumab (Avastin, Roche/Genentech) two to four days before surgery. We have a low threshold for cataract extraction before vitrectomy and prefer to avoid combined lensectomy/pars plana vitrectomy procedures.

First step

To start the case, we place 50% dextrose and viscoelastic on the cornea, which helps to maintain a clear view. A hybrid 23-ga approach with a 27-ga instrument allows for more versatility with instrumentation. Newer beveled high-speed cutters perform better than ever at segmenting fibrovascular membranes close to the retina.

However, we still find tremendous value in using a blunt spatula to delaminate and vertical pneumatic membrane peeler-cutter scissors to dissect in tight planes (*Video*). A high-magnification lens can be very helpful for visualization and for avoiding iatrogenic breaks posteriorly. We use triamcinolone early on and again toward the end of the case to address any residual hyaloid that can serve as a scaffold for membrane reproliferation.

View the Video

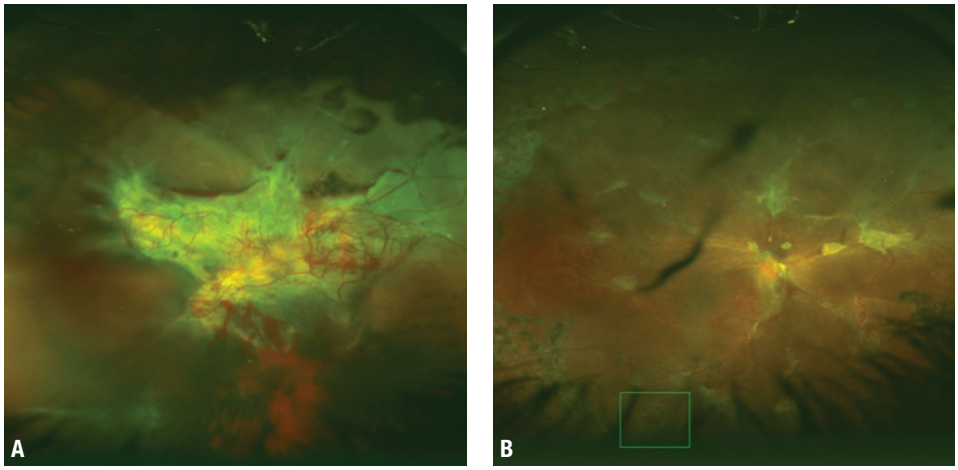


Watch as Drs. Komati and Skondra demonstrate tips for diabetic tractional retinal detachment repair. Available at: http://bit.ly/VideoPearl_016

Relieving traction

Patience and persistence are key to relieving the tractional forces on the retina during these cases. It's OK to leave residual pegs of fibrovascular membrane, as long as you address the associated traction. Sometimes the membrane may be too fused and inseparable from the retina and may require a focal retinectomy. If there are large

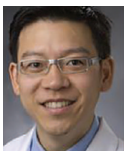
(Continued on page 35)



Preoperative photo of a diabetic tractional retinal detachment (A). At two months postop (B), the green box in the lower left quadrant shows the hole that was identified and barricaded, protected by gas.


Rahul Komati, MD


Dimitra Skondra MD, PhD


Paul Hahn, MD, PhD

Bios

Dr. Komati is the senior retina fellow in the department of ophthalmology and visual science, University of Chicago.

Dr. Skondra is associate professor of ophthalmology and visual science and director of the J. Terry Ernest Ocular Imaging Center, University of Chicago.

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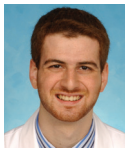
DISCLOSURES: Drs. Komati Skondra and Hahn have no relevant relationships to disclose.

Genetics in Retina

Gene therapy in AMD: Promises and challenges

Gene therapy could offer long-term stable control and prevent non-compliance, but the long-term effectiveness remains to be seen.

By Osama Sabbagh, MD, Ankur Mehra, MD, and Ramiro S. Maldonado, MD



Osama Sabbagh, MD

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Bios

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DISCLOSURES: The authors have no relevant financial relationships to disclose.

Take-home points

- While previously limited to monogenic inherited retinal diseases, gene therapies are now being explored for acquired or multifactorial diseases such as age-related macular degeneration.
- If successful, gene therapy could offer long-term stable control of vascular endothelial growth factor and prevent under-treatment.
- Significant challenges remain with retinal gene therapy, particularly with delivering the vector to the back of the eye.
- Long-term effectiveness of gene therapies in AMD remains to be seen, and the effect of chronic, constant suppression of VEGF may be a concern.

Gene therapy for the treatment of ocular disease has undergone significant development in recent years, particularly in the area of inherited retinal disease.[1] Ocular disease is a well-suited target for possible genetic therapies for a variety of reasons: the relative immune isolation of the eye; the availability of the contralateral eye as a control; the relative ease of treatment delivery; its enclosed structure; and the numerous methods of noninvasive outcome measures available.[1] Increasingly, age-related macular degeneration is emerging as a desirable, if somewhat complex, target for gene therapy.

Reasons for this go beyond AMD being a leading cause of blindness worldwide, although it's projected to affect approximately 196 million people in 2020.[2] Anti-VEGF intravitreal injections are far from perfect. The need for frequent visits and repeated injections is associated with a substantial burden on patients, family members and the health-care system.[1,3] Patient compliance with the required treatment schedules can be an issue. The cumulative risk of repeated intravitreal injections isn't insignificant; they include the risk of endophthalmitis, intraocular hemorrhage, retinal detachment, uveitis and ocular hypertension.[4]

Furthermore, anti-VEGF therapy isn't always efficacious. In the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), 34.1 percent of the monthly ranibizumab (Lucentis, Roche/Genentech) arm and 31.7 percent of the monthly bevacizumab (Avastin, Roche/Genentech) arm showed either no significant improvement or worsening of best-corrected visual acuity at one year.[5] While anti-VEGF injections offer a drastic improvement over previous options, newer therapies that offer higher efficacy or reduce the injection burden would certainly be a benefit.

A complex genetic profile

Compared to monogenic inherited retinal diseases, however, the pathogenesis of AMD is thought to be complex, with multiple genetic factors and environmental exposures contributing to the disease.[3] While multiple genes, such as CFH, CFB and ApoE, have been associated with the disease, our understanding of the genetic pathology of AMD remains incomplete. As such, the American Academy of Ophthalmology recommends avoiding routine genetic testing.[6] While the complex nature of AMD will likely require a multimodal approach, the potential role for gene therapy is strong, as evidenced by numerous recent and ongoing studies.[7]

Gene therapies require a method for delivery to the target cells. One popular method is the use of viral vectors, particularly adeno-associated virus (AAV).[8] This virus is attractive due to its lack of pathogenicity, multiple available serotypes, strong persistence despite a low-integration frequency and tendency to induce minimal host immune response, reducing the risk of destruction of the virus or transduced cells.[8]

Gene therapy and the FLT1 gene

The FLT1 gene encodes a member of the vascular endothelial growth factor receptor family, the tyrosine kinase receptors. These proteins bind to VEGF-A, VEGF-B and placental growth factor (PLGF), acting as natural VEGF inhibitors.[10] AAV2-sFLT01 (Sanofi/Genzyme) uses an AAV2 vector to deliver a gene that encodes the VEGF-neutralizing soluble Fms-related kinase-1 (sFLT-1).[10] It's given via intravitreal injection.

A Phase I open-label, dose-escalation trial in patients with wet AMD, subretinal fibrosis and vision worse than 20/100 reported no systemic side effects and ocular inflammation in only the highest-dose group.[10]

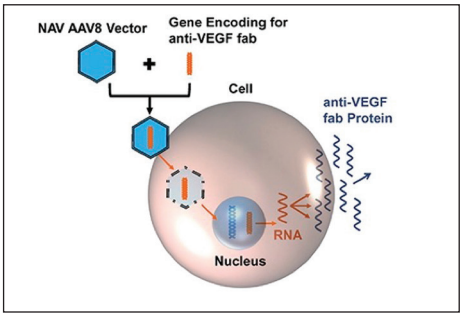

Figure 1. RGX-314 (RegenxBio) consists of an adeno-associated virus serotype 8 vector that delivers a gene encoding a monoclonal antibody fragment that binds vascular endothelial growth factor receptor-A. (*Courtesy RegenxBio*)

The trial demonstrated an anti-permeability effect, but also noted variability of expression with some, but not all, subjects showing response with reduction of intra- and subretinal fluid.[8,10] The variability has been attributed to pre-existing antibodies to AAV in some patients, which some authors have hypothesized limit transduction of target cells and thereby limit production of the desired protein.[10]

Similarly, a Phase I randomized controlled trial of subretinal injection of rAAV sFLT-1 reported that four of six patients in the treatment arm didn't require any anti-VEGF rescue injections.[11] Although it was a single-center study of only nine patients with relatively short follow-up, the trial demonstrated safety of the therapy. The results were maintained at 36 months.[12] Combined Phase I/IIa three-year results, comparing 24 treated patients and 13 controls, similarly showed a good safety profile.[13] However, because the study was designed to assess safety, it examined elderly patients with advanced disease and was unable to draw any significant conclusions regarding efficacy.[13]

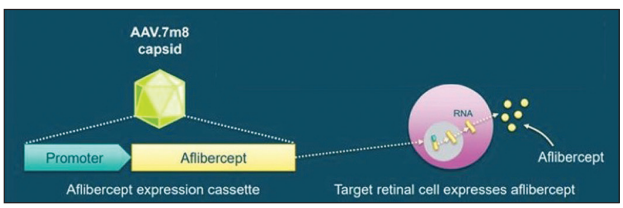

Figure 2. ADVM-022 (Adverum Biotechnologies) is an adeno-associated virus gene therapy vector for intravitreal injection that is a promoter of aflibercept protein expression. (*Courtesy Adverum Biotechnologies*)

Adeno-associated virus is attractive due to its lack of pathogenicity, multiple available serotypes, strong persistence despite a low-integration frequency and tendency to induce minimal host immune response.

RGX-314: AAV8, subretinal delivery

One gene therapy that recently completed Phase I/IIa trials for the treatment of wet AMD is RGX-314 (RegenxBio).[7,9] It consists of an AAV serotype 8 vector delivering a gene that encodes a monoclonal antibody fragment that binds VEGF-A (*Figure 1, page 17*).[8,9] The treatment requires a pars-plana vitrectomy to deliver the vector via subretinal injection, with the goal of transducing the retinal pigment epithelium.[8,9]

It's designed to induce the sustained production of a VEGF-binding antibody within the retina, leading to wet AMD disease control.[8,9] In the clinical trial, each patient received one treatment and was monitored for 12 months. The treatment appeared safe and reduced the need for other anti-VEGF treatments for more than one year after administration.[8,9] Researchers are preparing to start Phase IIb trials of RGX-314.[3]

ADVM-022 in-office gene therapy

ADVM-022 (Adverum Biotechnologies) is a novel recombinant AAV optimized for intravitreal administration and more robust protein expression.[14] Compared to previous modalities, it utilizes the AAV2.7m8 capsid, which has highly efficient retinal transduction, and is designed to result in strong expression of the aflibercept protein.[14] It can be administered via an intravitreal injection in an office setting (*Figure 2, page 17*).[14]

The OPTIC trial is an ongoing two-year, multicenter, prospective Phase I study evaluating the safety and tolerability of ADVM-022.[15] A single intravitreal injection is given seven to 14 days after a screening aflibercept injection (Eylea, Regeneron Pharmaceuticals) with a concurrent 13-day topical or oral corticosteroid course for control of inflammation. Szilard Kiss, MD, reported 24-week data at the Retina Society in September 2019 that showed a good safety profile, with mild to moderate inflammation as the only adverse event noted in all patients—although the inflammation was controlled with corticosteroids. Efficacy at 24 weeks seemed promising, with no patients needing rescue injections of anti-VEGF.

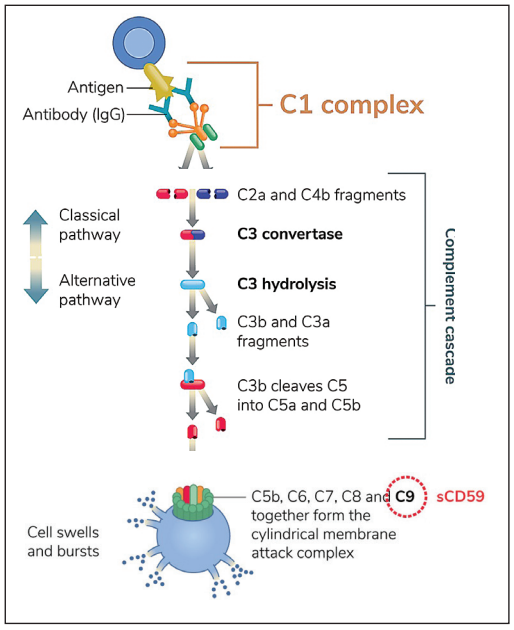

Figure 3. HMR59 (Hemera Biosciences), or AAVCAGsCD59, targets the complement cascade to inhibit the membrane attack complex. (*Courtesy Hemera Biosciences*)

Non-neovascular AMD gene therapy

Another gene therapy for AMD, HMR59 (Hemera Biosciences), or AAVCAGsCD59, is designed to affect the complement pathway via inhibition of its end product, the membrane attack complex (MAC).[8] Several studies have linked the complement pathway and MAC formation with AMD—with MAC-mediated release of growth factors thought to contribute to choroidal neovascularization and conversion to wet AMD.[8,16]

Administered as a single intravitreal injection, HMR59 uses an AAV2 vector and is designed to lead to production of a form of the CD59 protein, which binds the incomplete MAC and prevents binding of the C9 proteins required to complete the complex.[8] A Phase I trial assessing it in treatment-naïve wet AMD patients is currently underway (*Figure 3*).[8,17]

Because it affects the complement cascade, HMR59 also has the potential to treat dry AMD,[8] which could be impactful given the lack of effective treatments, particularly for advanced dry AMD with geographic atrophy.[3] Given this potential, HMR59 is also the subject of a Phase I trial for the treatment of advanced dry AMD, and early results have been promising.[17]

Another gene therapy currently in trials is GT005 (Gyroscope Therapeutics). Similar to HMR59, it uses an AAV vector and is designed to control complement activation.[18] It's delivered via subretinal injection. Current Phase I/II trials are evaluating its

effectiveness in advanced dry AMD with macular atrophy.[18]

Challenges of gene therapy

Despite the promise of gene therapy, significant challenges remain, particularly with delivering the vector. Most research utilizes AAV vectors, and while they have many advantages, concerns have persisted over their ability to effectively transduce cells, particularly when given intravitreally.[8] Subretinal delivery may be more effective, but has been associated with higher risks, such as damage to the retina and cataract formation.[8,14] The current capacity of AAV vectors is also limited, at approximately 4.7 kb.[8]

Long-term effectiveness of these therapies remains to be seen, and the effect of chronic, constant suppression of VEGF is a concern.[8] Finally, given the difficulty of manufacturing these treatments, the price of gene therapy remains high. If future AMD therapies have similar costs, it may place a substantial burden on patients and the health-care system.

Bottom line

Gene therapy may have a substantial impact in AMD due to the high prevalence of the disease, the lack of effective treatments for advanced dry AMD and the treatment burden of wet AMD. Such multifactorial, non-monogenic diseases will likely warrant a combination of therapies, and novel targets and pathways of treatment will need to be identified. If successful, gene therapy could offer long-term stable VEGF control and prevent undertreatment from patient non-compliance in AMD. RS

Table. Investigative gene therapies for age-related macular degeneration

Therapy name (sponsor)	Vector	Indication	Study Phase	Mechanism of action	Delivery method
RGX-314 (RegenxBio)	AAV8	Neovascular AMD	I/IIa	Encodes an anti-VEGF Fab protein similar to ranibizumab.	Surgical subretinal injection
ADVM-22 (Adverum Biotechnologies)	AAV2	nAMD	I	Promotes production of aflibercept protein.	Intravitreal injection
AAV2-sFLT01 (Sanofi/ Genzyme)	AAV2	nAMD	I	Encodes sFLT-1 to neutralize vascular endothelial growth factor.	Intravitreal injection
AAVCAGsCD59 or HMR59 (Hemera Biosciences)	AAV2	nAMD and non-nAMD	I	Soluble form of CD59 to inhibit membrane attack complex formation.	Intravitreal injection
GT005 (Gyroscope Therapeutics)	AAV2	Non-nAMD	I/II	Targets complement cascade.	Surgical subretinal injection

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Genetics in Retina

Gene therapy and editing for the retina: A primer

A look at advances in gene replacement therapy, gene delivery and CRISPR technology.

By Sook Hyun Chung, PhD, and Glenn Yiu, MD, PhD

Sook Hyun Chung, PhD

Glenn Yiu, MD, PhD

Take-home points

- Gene replacement therapies have shown success for treating recessive inherited retinal diseases, with one therapy already approved and others the subject of current clinical trials.
- New target genes, viral vectors, and delivery routes may expand the spectrum of IRDs that can be treated with gene therapy.
- CRISPR-based genome editing holds the promise for treating dominant IRDs in preclinical studies, but further investigations are required to address potential immunogenicity and off-targeting.

Bios

Dr. Chung is a project scientist at University of California, Davis, in Sacramento. Her current project includes preclinical studies to develop potential gene therapies for neovascular age-related macular degeneration using CRISPR-based genome editing.

Dr. Yiu is an associate professor of ophthalmology at UC Davis. He is a retina specialist and clinician-scientist, with a translational research program focused on AMD through ocular imaging, genome editing and gene therapy, and nonhuman primate models.

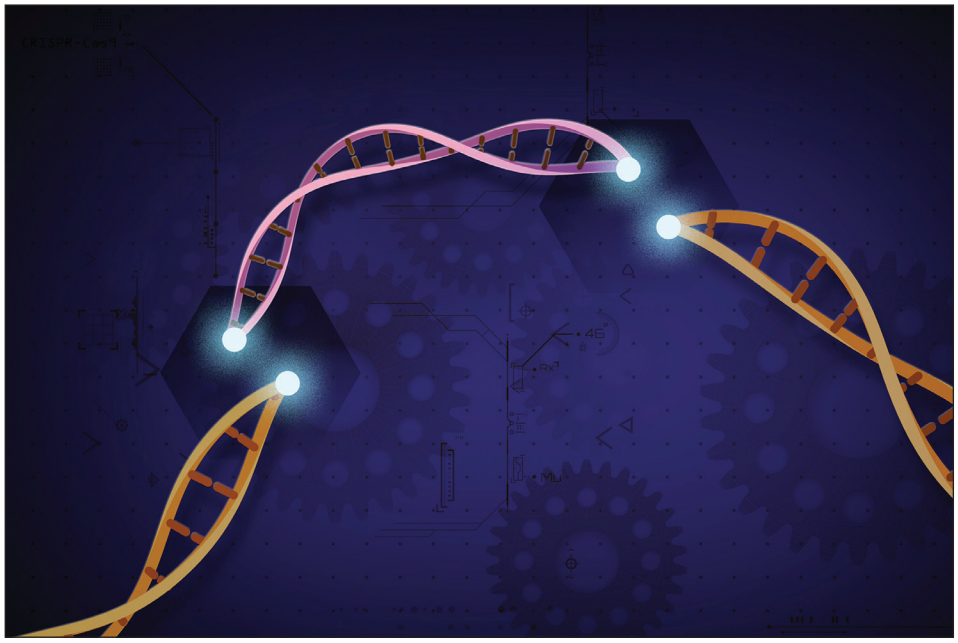
Inherited retinal diseases affect approximately 200,000 people in the United States and 4.5 million people worldwide.[1] Most IRDs are caused by mutations in single genes that may be amenable to gene therapy. However, while IRDs have been historically classified based on clinical features and electroretinography, genetic testing has revealed that many different genetic mutations can cause each IRD. Because most current gene therapies target a specific gene or gene mutation, the heterogeneity of IRDs requires a wide array of different treatment strategies to be developed.

Compared to pharmacologic agents, gene therapies have the potential advantages of long-term therapeutic effects and capacity for cell-targeted therapy; for example, by using cell-specific promotors. The term "gene therapy" typically refers to gene-replacement therapy, where a normal, functional copy of a gene is introduced to replace the mutated gene. However, gene-replacement therapies are useful mainly for recessive IRDs, where neither of the two mutated alleles can produce functional gene products.

By contrast, dominant IRDs are not amenable to gene replacement because the mutant gene product interacts or interferes with normal protein function, even if an exogenous source produces it. Instead, dominant IRDs must be treated by inactivating the mutant protein or ablating the mutant gene at the DNA level; for example, by using CRISPR-based genome editing.

Gene-delivery strategies

Both gene-replacement and genome-editing therapies require the transfer of genetic materials to host cells, which can be accomplished using viral or non-viral methods. Many viruses have naturally evolved to infect human cells, and can be engineered to carry a therapeutic transgene. The desired characteristics of gene-delivery vectors include high expression, long durability, large capacity, low



Cover image. Artist's rendering of gene editing, depicted as a tool to enable precise cuts of double-stranded DNA, which can be allowed to either cause targeted mutations or substitution with similar sequences of DNA. (*Ernesto del Aguila III, National Human Genome Research Institute, National Institute of Health*)

immunogenicity and low risk of mutagenicity (*Table 1*). The important gene-delivery vectors are:

- ***Lentiviruses,*** which can deliver approximately 8-kilobase (kb)-long DNA sequences for long-term expression, but this process has a mild risk of mutagenesis because it integrates into the host genome.
- ***Adenoviruses***, which do not integrate, but are limited by their short durability and high immunogenicity that can cause uveitis.
- ***Adeno-associated viruses (AAVs)***, the most common platform because they are non-pathogenic and non-integrating. AAVs with different capsid serotypes can target different cell types, with intravitreal AAV2 and AAV8 infecting retinal ganglion cells, and subretinal AAV2, AAV5, AAV7, AAV8 and AAV9 transducing photoreceptors and RPE.[2–5] AAVs have a limited carrying capacity of approximately 4.7 kb, so larger genes such as the ABCA4 gene for Stargardt disease cannot be delivered using a single AAV vector.
- ***Non-viral approaches***, such as synthetic polymers and nanoparticles, are generally safe, but are not as effective for gene transfer as viruses.

Delivering vectors

Vectors are generally delivered by subretinal or intravitreal injections. Intravit-

Table 1. Types of virus used as transgene mediators for trans-gene therapy

Characteristic	Lentivirus	Adenovirus	AAV	Synthetic
High expression	✓	✓	✓	Low expression
Long duration	✓	Short-lived	✓	unknown
Large capacity	✓	✓	Small cargo	unknown
Low immunogenicity	✓	Uveitis	✓	✓
Low risk of mutations	Integrating	✓	✓	✓

Disclosures

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real injections are easier to perform, but most AAV cannot penetrate the internal limiting membrane to reach the outer retina. Subretinal injections can overcome the ILM barrier, but they require invasive vitrectomy surgery and the therapeutic effect is limited to the small area of the subretinal bleb.

Newer generations of AAV developed by "directed evolution" have shown promise in crossing the ILM from the vitreous, and are in clinical trials. Our laboratory recently demonstrated the possibility of suprachoroidal AAV delivery using micro-needles, which provide widespread but mostly peripheral transgene expression that may be useful for "biofactory" therapies such as production of anti-angiogenic factors. Compared with intravitreal and suprachoroidal delivery, however, the subretinal space is immune-privileged and is less prone to triggering intraocular inflammation.[5]

Gene-replacement therapies

• ***Type 2 Leber congenital amaurosis.*** The best-known ocular gene therapy is for the treatment of type 2 LCA. LCA is an autosomal recessive IRD that occurs in one in 80,000 births, and is associated with mutations in the GUCY2D, CEP290 and RPE65 genes.[6] RPE65 is involved in the production of 11-cis retinal during phototransduction, and accounts for 5 to 10 percent of LCA cases.[7] In animal models including RPE65-deficient mice and

Table 2. Completed and on-going clinical trials in inherited retinal disease

Sponsor	Phase	Therapy	Start Date	Status
Choroideremia				
Spark Therapeutics	I/II	Subretinal AAV2-hCHM x2	January 2015	Open-label trial of 15 participants. Enrollment completed. Completion date 2032.
NightstaRx Ltd./ Biogen	III	Subretinal rAAV2.REP1	December 2017	Interventional nonrandom trial of 15 participants. Enrollment completed. Completion date 2032.
Stargardt Disease				
Sanofi	II	Subretinal lentiviral ABCA4	June 2011	Open-label, nonrandomized trial of 27 participants terminated in 2019.
Achromatopsia				
Applied Genetics Technology Corp. (AGTC)	I/II	Subretinal rAAV2tYF-PR1.7-hCNGB3	February 2016	Open-label, nonrandomized trial of 24 participants currently recruiting. Completion date 2024.
AGTC	I/II	Subretinal AGTC-402 (CNGA3)	May 2017	Open-label, nonrandomized trial of 24 participants currently recruiting. Completion date 2023.
X-linked Retinitis Pigmentosa				
NightstaRx Ltd./ Biogen	II/III	Subretinal AAV8-RPGR	March 2017	Randomized trial of 63 participants currently recruiting. Completion date August 2020.
AGTC	I/II	Subretinal rAAV2tYF-GRK1-RPGR	April 2018	Nonrandomized, open-label trial of 30 participants currently recruiting. Completion date 2025.
X-linked Retinoschisis				
AGTC	I/II	Subretinal rAAV2tYF-CB-hRS1	May 2015	Nonrandomized, open-label trial of 27 participants. Completion date 2023. Active, not recruiting.

dogs, subretinal AAV2-mediated RPE65 delivery improved visual function[8-10] and, despite relatively modest efficacy in early human trials,[11,12] demonstrated safety and benefit in Phase III studies which led to its approval by the Food and Drug Administration in 2017 (Luxturna, Spark Therapeutics).[13]

• ***Choroideremia.*** This X-linked recessive IRD occurs in one in 50,000 males.[14] Symptoms include night blindness and gradual vision loss beginning in childhood. The CHM gene encodes the Rab escort protein 1 (REP1) essential for intracellular vesicular transport.[15] Subretinal AAV2-REP1 in CHM knockout mice demonstrated improvements in electroretinogram,[16] and Phase I/II trials have shown improved visual acuity in some patients with no significant adverse effects.[17,18] Phase II trials began in 2015 and are ongoing in patients with early choroideremia.

• ***Stargardt disease.*** This autosomal recessive macular atrophy has a prevalence of one in 10,000 people.[19] The disease-causing ABCA4 gene encodes a transmembrane protein in photoreceptor outer segments, and its dysfunction results in accumulation of toxic A2E byproducts that accumulate in the retinal pigment epithelium leading to photoreceptor death.[20]

Nonsense mutations cause early onset disease in childhood with more severe atrophy, whereas missense variants are usually adult-onset, often sparing the fovea.[21] The current Phase II trial employs a lentiviral vector due to the large size of the ABCA4 gene,[22] although preclinical studies using a hybrid dual AAV system also show promise in ABCA-/- mice.[23](p4) Gene therapies for many other IRDs are under development (*Table 2*).

CRISPR-based genome editing

Unlike conventional gene replacement therapy, genome editing using Clustered Regularly Interspaced Palindromic Repeats (CRISPR) technology enables treatment of dominant IRDs by targeting genetic mutations at the DNA level. Unlike previous genome surgery tools like TALEN or zinc finger nuclei, which are time-consuming and expensive to develop, CRISPR-based treatments can be quickly designed and easily generated.

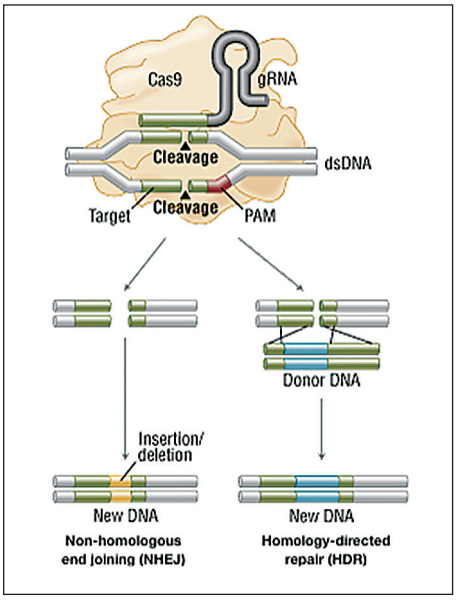

Figure 1. The CRISPR Cas9 repairing mechanisms involve Cas9 nuclease/gRNA complex recognizing a specific DNA site and inducing a double-strand DNA (dsDNA) break. It can be repaired by non-homology end joining, resulting in indels or homology directed repair (HDR) that induce gene replacement/ knock-in. (*Reprinted from www.neb.com (2020) with permission from New England Biolabs*)

CRISPR systems were first discovered in prokaryotes as part of their adaptive immune system against viral invasion. Bacteria infected by bacteriophages incorporate viral DNA fragments into their genome, which can be transcribed to guide RNA (gRNA) to program CRISPR-associated endonucleases, such as Cas9, to cut these foreign DNA sequences upon future encounters.

By designing gRNAs to program Cas9 enzymes to precisely cut a target gene locus,[24,25] CRISPR can be used to:

CRISPR technology enables treatment of dominant inherited retinal diseases by targeting genetic mutations at the DNA level. CRISPR-based treatments can be quickly designed and easily generated.

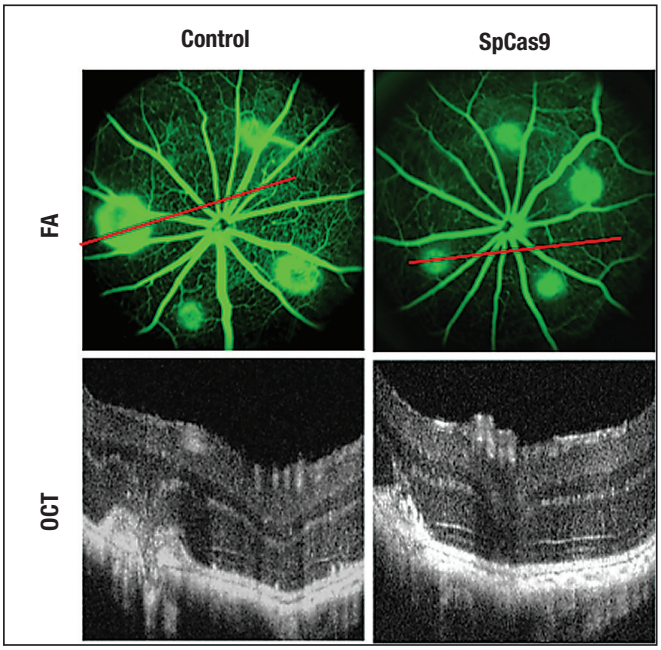

Figure 2. Reduction of laser-induced choroidal neovascularization in a mouse retina injected with AAV8-expressing SpCas9. Fluorescein angiography and optical coherence tomography images show suppression of CNVs in the eye injected with SpCas9 (right column), compared with the control retina (left column).

- ablate a normal gene or destroy a dominant mutant allele by allowing natural, error-prone DNA repair processes that result in insertion or deletion of several nucleotides to cause frameshift mutations (indels); or
- repair a mutated gene by providing a DNA template of the normal gene that can be incorporated through a process known as homology directed repair (HDR) (*Figure 1, page 23*). Current applications are mostly limited to gene ablation, as HDR is much less efficient.

Given the bacterial origin of CRISPR systems and the permanent impact of genome editing, potential host immune responses and off-target effects require thorough investigation before human trials commence.

Early results of CRISPR genome editing

Use of CRISPR-based genome editing in IRDs has demonstrated success in animal models. One approach is by deactivating the rhodopsin mutations in rodent models of autosomal dominant retinitis pigmentosa.[26–28] Another is by destroying the dominant mutation in the CEP290 gene in LCA type 10 models.[29–31]

Subretinal AAV delivery of this CRISPR-based strategy for LCA10 is being evaluated in Phase I/II studies. Given the heterogeneity of different disease-causing mutations, another promising approach is an "ablate-and-replace" strategy that couples CRISPR-based ablation of the endogenous rhodopsin gene in a mutation-independent manner with exogenous expression of the wild-type rhodopsin.[28]

Our laboratory has also been investigating the use of CRISPR for neovascular AMD, since genomic ablation of the VEGFA gene would provide a permanent cure that contrasts with the frequent and costly anti-VEGF treatments that are currently in wide use. We first demonstrated the use of CRISPR-Cas9 to suppress VEGF from human cells *in vitro*,[32] and more recently, in mouse models of choroidal neovascularization (CNV) *in vivo* (*Figure 3*).[33]

Bottom line

Gene replacement therapy has shown some success for recessive IRDs, with the first approved therapy for type 2 LCA and many other trials underway. Advances in gene delivery, such as new generations of AAV and suprachoroidal delivery, may further improve effectiveness. By manipulating the genome at the DNA level, CRISPR technology holds the promise of permanently curing dominant IRDs,

(Continued on page 37)

DRCR Protocol V in the real world

Here's why we should feel more confident observing patients with center-involving diabetic macular edema with good vision.

Mustafa Safi, MD, and Roger A. Goldberg, MD, MBA

Take-home points

- The DRCR Retina Network Protocol V study addresses management of center-involving diabetic macular edema in patients with good vision, randomizing patients to observation, focal laser or intravitreal aflibercept.
- For eyes with center-involving DME and visual acuity of 20/25 or better, observation with close follow-up may be a reasonable initial management option and doesn't compromise visual acuity outcomes at two years.
- Close follow-up is important, as patients were followed every eight to 16 weeks and rescued with aflibercept if their vision declined.
- As with any good trial, addressing one clinical question raises new ones. Retina specialists will be challenged to apply the Protocol V results to real-world clinical practice.

Mustafa Safi, MD

Roger Goldberg, MD, MBA

Despite advances in eye care, diabetic macular edema remains the most common vision-impacting complication of diabetic retinopathy and represents one of the major causes of visual impairment in the developed world.[1] With prolonged and poorly controlled blood glucose levels, the integrity of the microvasculature supplying the inner retina is compromised by inflammation and hyperglycemic-induced damage to pericytes, resulting in "leaky" vessels leading to retinal edema and thickening.[2–4] This excess permeability can be treated with intravitreal anti-VEGF injections, which have become a mainstay of care for patients with visually significant DME.

What's 'visually significant' DME?

But, what is "visually significant" DME? The historic term "clinically significant macular edema" (CSME) was defined in the Early Treatment of Diabetic Retinopathy Study as a clinical diagnosis based on the exam findings, not optical coherence tomography or visual acuity results.[5] Advances in imaging technology, particularly with the ubiquity of OCT, have allowed clinicians to detect more subtle DME, often before patients have appreciated a decline in visual acuity or visual function. In fact, one study showed more than 80 percent of patients with DME have a visual acuity of 20/40 or better.[6]

High-quality, randomized, masked studies such as RISE and RIDE (leading to the approval of ranibizumab [Lucentis, Roche/Genentech]), or VIVID and VISTA (aflibercept [Eylea, Regeneron Pharmaceuticals]), excluded patients with good vision, leaving retina specialists uncertain about how to manage patients with DME and good vision. Thankfully, the DRCR Retina Network has stepped in to help address this important ques-

Bios

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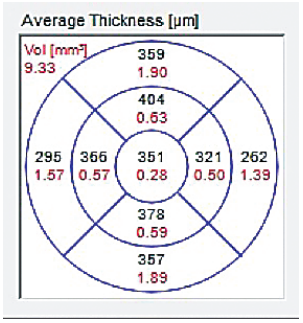

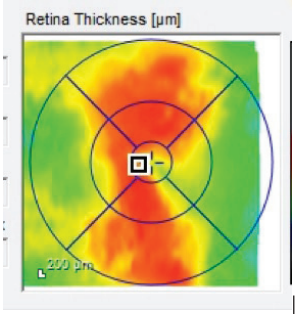

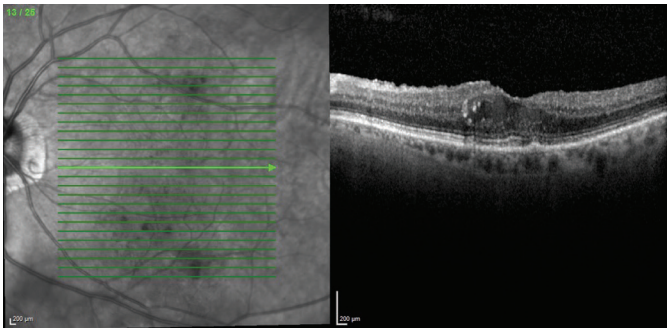

This patient has center-involving diabetic macular edema with corrected 20/30 vision, improving to 20/20 through pinholes. Central subfield thickness is 351 µm. DRCR Retina Network Protocol V gives insight on how to manage such a patient with DME and good vision, though questions remain. For example, this patient said that she felt her vision in this eye had worsened. Two months earlier, the in-clinic vision measured the same, but the central retinal thickness was 283 µm. (*Image courtesy Bay Area Retina Associates, Walnut Creek, Calif.*)

tion with Protocol V, assessing treatment options for patients with DME and "very" good vision. [7]

Protocol V design and findings

This was a multicenter, randomized trial that took place from 2013 to 2018. Patients with center-involving DME greater than 250 µm on time-domain OCT and an ETDRS best-corrected visual acuity of 20/25 or better were enrolled. Subjects were randomized to one of three arms: aflibercept injections; focal/grid laser photocoagulation; or observation.

The primary outcome of the study was investigating the proportion of patients who lost at least one line (5 letters) of vision at two years. Patients were followed every eight to 16 weeks. Those randomized to the focal/grid laser photocoagulation and observation arms were allowed to be rescued if the visual acuity deteriorated by two lines or more during any visit or by one to two lines during two consecutive visits.

Across all arms, the proportion of patients who lost at least 5 letters of visual acuity at two years was similar with 16-, 17- and 19-percent declines in the aflibercept, laser/grid photocoagulation and observation arms, respectively (p=0.79). Also, 25 percent of patients in the photocoagulation group and 34 percent in the observation group received intravitreal aflibercept for significant visual acuity decline according to the study's rescue parameters. The median number of injections in the laser and observation groups were seven and nine, respectively, for those who required rescue. After two years of follow-up, VA across all groups was comparable, with a mean of 20/20.

Real-world implications

These results suggest that patients with CI-DME and good vision (20/25 or better) can be managed initially with observation and close follow-up. This is important information for retina specialists and patients alike, and can provide the opportunity for clinicians to spend the time educating their patients on diabetic retinopathy and the importance of blood-sugar and blood-pressure control.

However, as with any good study that seeks to answer a particular question, Protocol V raises several new questions as we try to apply these trial results to the clinical setting. They include:

• ***Clinic vision vs. ETDRS vision.*** In a busy clinical setting, many factors can affect the measured VA, including the exam lane used, the technician performing the assessment, whether the patient brought his or her glasses that day, whether pinhole measurement is used, the patient's motivation, the severity of his or her dry-eye symptoms that day, etc.

How should we interpret the normal fluctuations in vision that can occur in patients, when the clinical exam and/or

imaging remain unchanged? In addition, for those of us who participate in clinical trials, we know that 20/25 ETDRS vision is very different than 20/25 clinic vision. Typically, the ETDRS vision is better than the vision measured in the clinic. Should we therefore extrapolate Protocol V findings to patients with 20/30 or 20/40 vision?

• ***Other factors that impact vision.*** What should we do for patients with CI-DME and a cataract? Or ocular surface disease? Sometimes it can be difficult to tell which factors are contributing to the visual decline.

• ***Progressive disease.*** The retreatment criteria in Protocol V were visual acuity-based. Given the challenges listed earlier with clinic visual acuities, how should we respond to the patient whose DME is worsening on OCT? Or if his or her peripheral diabetic retinopathy is worsening? Sometimes, even if we don't routinely treat nonproliferative diabetic retinopathy with anti-VEGF injections, we may be more prone to do so when DME is present, even with good vision.

• ***Follow-up intervals.*** Clinical trials have predefined schedules for evaluation that often are more frequent than what's practical in the real world. In addition, patients who participate in clinical trials understand the commitment they are making over a one- or two-year period. Many patients choose not to participate in trials because the commitment is too burdensome. For these patients who cannot commit to Protocol V's close follow-up standards, how should we extrapolate the safety of observation, particularly when one-third of observed patients ultimately required some treatment?

• ***Improved to 20/25.*** Protocol V enrolled patients who had treatment-naïve DME. But, what about the huge cohort of patients who are treated for DME and improve their vision to Protocol V standards (i.e., 20/25 or better)? Can we then safely observe them until their vision declines again? Or should we continue with regular treatment based on the algorithms of prior studies like RISE, RIDE, VIVID, VISTA or DRCR Protocols I and T?[8,9]

Bottom line

The DRCR Retina Network plays a critical role in helping to address important clinical questions in the management of diabetic retinopathy. Often, these are studies that drug manufacturers may not be motivated to support directly. Protocol V aimed to answer one such question: How should we manage patients with good vision despite center-involving DME on exam and OCT?

Based on the results of Protocol V, clinicians should feel more confident if they decide to observe these patients while following them closely. Like most great studies, and perhaps it's always the case, understanding one thing better opens up a whole new line of questions, some of which may never be fully answered. We will then have to apply these scientific results to the individual patient sitting in the exam chair in front of us. In this way, the art of medicine lives on. RS

As with any good study that seeks to answer a particular question, Protocol V raises several new questions as we try to apply these trial results to the clinical setting.

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When to operate on RVO and when to (mostly) not

The side-effect profile is significant, but a few approaches may help to extend medical treatment in selected cases.

Durga S. Borkar, MD,

Sharon Fekrat, MD, FACS

By Durga S. Borkar, MD, and Sharon Fekrat, MD, FACS

Take-home points

- Studies have reported discouraging outcomes for at least three surgical techniques targeting specific pathology in eyes with retinal vein occlusion.
- Pars plana vitrectomy with removal of the posterior hyaloid may decrease retinal thickness and improve visual acuity in some eyes.
- Adding internal limited membrane peeling may confer anatomic benefits; however, the functional benefits aren't so clear.
- Any anatomical improvement from pars plana vitrectomy with or without ILM peeling should be balanced with the likelihood of associated visual improvement.

Bios

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Dr. Fekrat is a retina specialist and surgeon at the Duke Eye Center and professor of ophthalmology and associate professor of surgery at Duke University School of Medicine.

DISCLOSURES: Dr. Borkar has received consulting fees from Genentech.

Dr. Fekrat receives patent royalties from Alcon.

After diabetic retinopathy, retinal vein occlusion is the second most common retinal vascular disease and carries a significant risk of vision loss, particularly when untreated, due to associated sequelae including macular edema, retinal ischemia and neovascularization. In the majority of cases, first-line treatment for macular edema is intravitreal injection of anti-VEGF. In some eyes, intravitreal corticosteroid is subsequently incorporated.

However, RVO-associated macular edema often recurs when the pharmacologic agent has worn off, requiring repeated and often monthly injections for disease control. In the last two decades, several surgical techniques have been described for the management of eyes with RVO, typically targeting the anatomic sites implicated in the pathoetiology of RVO, but they have largely fallen out of favor.

This article reviews variable study results of six different surgical techniques for treating RVO and provides insight into the few cases for which surgery may be considered.

Vitrectomy with arteriovenous sheathotomy

Since venous compression at the site of an arteriovenous crossing may predispose to branch retinal vein occlusion, surgical management has been geared toward this site of pathology. Pars plana vitrectomy with arteriovenous (AV) sheathotomy was first described in 1988 and again in 1999.[1,2]

With this technique, a standard three-port PPV is performed followed by the use of a microvitreoretinal blade to incise and dissect open the AV sheath between the vessels at the etiologic arteriovenous crossing to release the branch retinal vein from the artery to improve venous outflow at the site of the occlusion (*Figure 1*). Fluorescein angiography is often used preoperatively

to identify the best AV site to target.

While initial studies of this technique were promising, further studies showed that even though up to one-third of eyes had resolution of macular edema and some visual improvement in some series,[3,4] complications were not uncommon. They included localized retinal detachment at the site of the sheathotomy.[3] In most cases, venous outflow didn't improve and visual results were lackluster. Given the lack of reproducible substantial visual acuity gains, AV sheathotomy is rarely performed in 2020.

Vitrectomy with radial optic neurotomy

In eyes with central retinal vein occlusion, many authors have described a type of "compartment syndrome" at the scleral outlet. They proposed that relieving this outlet obstruction by performing vitrectomy with radial optic neurotomy (RON) could improve venous outflow in these eyes.[5-7]

This approach involves performing a standard three-port PPV and then making a radial incision at the rim of the nasal side of the optic nerve to incise the scleral ring and decompress the presumed scleral outlet obstruction, thus improving venous outflow in the central retinal vein (*Figure 2, page 30*).

Some of these studies reported significant improvement in visual acuity.[5-7] However, most eyes that underwent RON did not have improved vision. Additionally, adverse events including choroidal neovascularization at the RON site have been reported.[6] It's also unclear if vitrectomy with removal of the posterior hyaloid alone leads to resolution of the macular edema and improved visual outcomes in these cases, rather than the effects of the RON itself.[5]

Chorioretinal anastomosis with or without vitrectomy

A third surgical technique that has been described to improve retinal perfusion through direct anatomic intervention in eyes with both CRVO and BRVO is the creation of a chorioretinal anastomosis. The thought is that making a connection between a retinal vein and the choroidal venous circulation may create a venous detour so that venous outflow can bypass the occluded retinal vein.

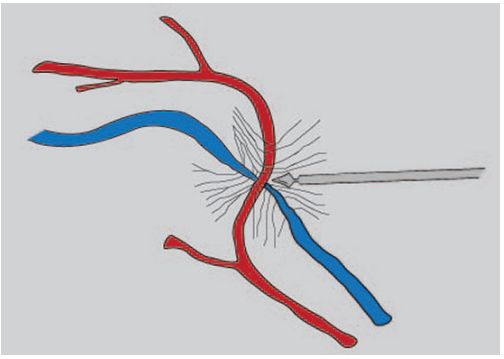

Figure 1. Arteriovenous sheathotomy involves a standard three-port pars plana vitrectomy and then incision of the arteriovenous sheath between the vessels at the etiologic arteriovenous crossing site with a microvitreoretinal blade to release the branch retinal vein from the artery and improve venous outflow at the site of the occlusion.

While this could be performed in the clinic with application of laser pulses to rupture the wall of a branch vein and adjacent Bruch membrane to promote anastomosis formation during the healing process, a chorioretinal anastomosis can also be created during standard three-port PPV and posterior hyaloid detachment using transvitreal venipuncture.[8]

However, the side effects of this technique are potentially significant. They include preretinal fibrosis, segmental retinal ischemia and choroidovitreal neovascularization, so this surgical technique has not been widely adopted. If creation of a chorioretinal anastomosis is sought in select eyes, laser in the clinic is often the method of choice to do so.

Vitrectomy with retinal vein cannulation

Surgical retinal vein cannulation during vitrectomy surgery in eyes with CRVO has also been explored with promising improvements in visual acuity.[9] Because histopathologic studies have demonstrated a thrombus at the level of the lamina cribrosa in eyes with CRVO, targeted retinal venous cannulation can allow direct access to the

The side effects of chorioretinal anastomosis are potentially significant and include preretinal fibrosis, segmental retinal ischemia and choroidovitreal neovascularization.

thrombus, which may be displaced with injection of balanced salt solution alone or dissolved with recombinant tissue plasminogen activator, ocriplasmin (Jetrea, Oxurion) or other thrombolytic.

Animal studies are evaluating retinal cannulation for the treatment of RVO, both unassisted and with robotic assistance for more distal, difficult-to-access vasculature.[10,11] Recently, a report of four RVO patients undergoing robot-assisted retinal vein cannulation was published, showing both technical feasibility and a reasonable safety profile.[12]

Vitrectomy with and without ILM peeling

Prior studies have evaluated the role of vitrectomy with removal of the posterior hyaloid with and without internal limiting membrane peeling to treat macular edema associated with RVO, particularly when the edema is refractory to treatment with intravitreal anti-VEGF or corticosteroid therapy.

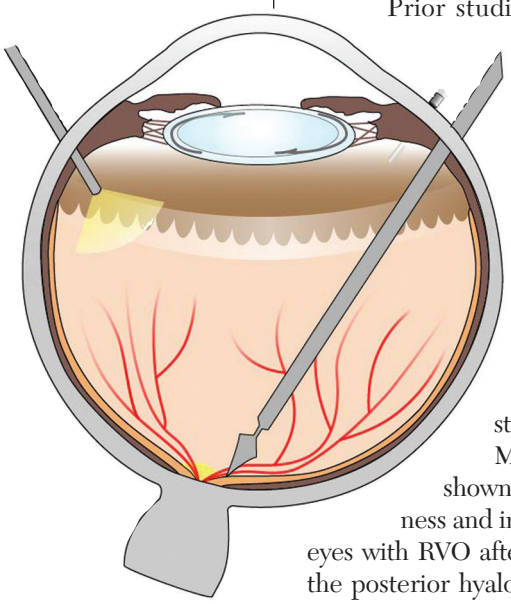

Figure 2. In radial optic neurotomy, after a standard three-port pars plana vitrectomy, a radial incision is made at the rim of the nasal side of the optic nerve using a microvitreoretinal blade to incise the scleral ring and decompress the presumed scleral outlet obstruction, thus improving venous outflow in eyes with central retinal vein occlusion.

Multiple studies have shown decreased retinal thickness and improved visual acuity in eyes with RVO after PPV with removal of the posterior hyaloid alone, without ILM peeling.[13-15] Prior studies have suggested that the vitreous may be a reservoir for inflammatory and growth factor mediators, including interleukin-6 and vascular endothelial growth factor.[16-18] Therefore, removal of the vitreous alone may lead to resolution of macular edema on a cellular level with reduced retinal hypoxia, decreased vascular permeability, and improved oxygenation of the inner retina as more oxygenated aqueous fills the vitrectomized vitreous cavity.[19]

In one study, eyes with higher preoperative intravitreal anti-VEGF levels had less visual acuity gains after PPV.[15] This suggests that there may be a correlation and the potential to predict which eyes with RVO will be most responsive to surgical management in the future.

While ILM peeling is thought to primarily relieve mechanical forces contributing to macular edema, such as tangential traction, the added step of ILM peeling may provide the extra benefit of decompression of the inner retina.[20] Furthermore, removal of the ILM may also possibly decrease macular edema by stimulating a neural repair process.[21] While ILM peeling may confer anatomic benefits, whether or it provides a functional benefit is still up for debate.

The largest study of this approach, the European VitreoRetinal Society Macular Edema Study, evaluated visual acuity outcomes in a nonrandomized fashion at 24 months postoperatively following PPV with ILM peeling vs. treatment with intravitreal anti-VEGF or steroid injections. In more than 700 cases of CRVO or BRVO, the study reported significantly greater visual gains in eyes treated with surgical management.[22]

On the other hand, smaller retrospective case series have reported a decrease in retinal thickness without significant visual acuity gains in eyes with CRVO after PPV with ILM peeling.[23,24] These studies have shown heterogeneity in the time duration from development of RVO to surgery, extent of retinal ischemia, lens status and surgical technique. No randomized trial has evaluated the utility of PPV with or without ILM peeling for the treatment of macular edema secondary to RVO.

Pitfalls and potential of vitrectomy surgery in eyes with RVO

Reperfusion of the retina continues to be a primary goal in vitreoretinal surgical techniques for management of RVO. However, no definitive studies have reproduc-

ibly shown the visual benefit of vitrectomy with either AV sheathotomy, radial optic neurotomy, creation of a chorioretinal anastomosis or retinal vein cannulation thus far. Furthermore, the side-effect profile for all of these techniques includes vision-threatening complications, including choroidovitreal neovascularization, which may persist despite aggressive treatment in some eyes.

With the introduction of anti-VEGF treatment and corticosteroid options, these more invasive surgical options have become less common in the armamentarium of treatment options for eyes with retinal vein occlusion.

However, PPV, removal of the posterior hyaloid and possible ILM peeling may derive added benefit to existing treatments, particularly in cases of persistent macular edema that would otherwise require frequent intravitreal treatment. The half-life of intravitreal anti-VEGF medications in vitrectomized eyes is shorter than in non-vitrectomized eyes, so they clear faster and have decreased efficacy.[25] Thus, longer-acting adjuvant treatment, such as more durable anti-VEGF agents or corticosteroids, may need to be considered after PPV in eyes with RVO.

Bottom line

The known anatomical improvement from PPV with or without ILM peeling should be balanced with the likelihood of associated visual improvement. We should consider this in the context of several other factors, such as retinal perfusion status, the length of time since the initial event and concurrent ophthalmic comorbidities that may limit visual acuity. RS

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PPV, removal of the posterior hyaloid and possible ILM peeling may derive added benefit to existing treatments, particularly in cases of persistent macular edema that would otherwise require frequent intravitreal treatment.

Is drier better in neovascular AMD?

It may depend on the location of the fluid. A quick look at HARBOR post-hoc results.

Nancy M. Holekamp, MD

Nancy M. Holekamp, MD

Take-home points

- Some neovascular age-related macular degeneration patients will have persistent fluid and good vision despite monthly anti-VEGF injections.
- Post-hoc HARBOR trial findings suggest a complex relationship between retinal fluid and functional outcomes.
- Existing and emerging evidence suggests a more nuanced view of fluid status and visual acuity outcomes is warranted.

When giving anti-VEGF injections for neovascular age-related macular degeneration, most retina specialists "treat to dry," whether using monthly, bimonthly, *pro re nata* or treat-and-extend injection regimens. Since the beginning of the anti-VEGF era, retina specialists have collectively concluded that a "dry" retina—one resolved of intraretinal, subretinal or sub-retinal pigment epithelium fluid—would have a better visual acuity outcome than a "wet" retina, one with incompletely resolved fluid in any layer.

However, it's unclear if complete retinal fluid resolution is required for optimal vision outcomes. For example, some nAMD patients will have persistent fluid despite monthly injections and demonstrate good vision, perhaps even 20/20.

In fact, these patients seem to see as well as other patients who are completely dry and perhaps require less frequent injections. This raises the question: What's the relationship between retinal fluid and vision outcomes?

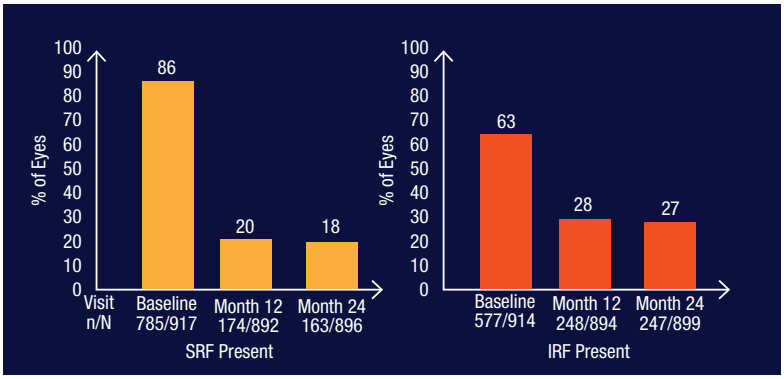

Figure 1. Fewer than 30 percent of eyes in the analysis group had residual subretinal (SRF) or intraretinal (IRF) fluid after 12 and 24 months of treatment with ranibizumab (Lucentis, Roche/Genentech).

Bio

Dr. Holekamp is director of retina services at Pepose Vision Institute, Saint Louis.

DISCLOSURES: Dr. Holekamp disclosed consulting, speaking and/or contract research relationships with Allergan, Acucela, Lineage Cell Therapeutics, Clearside Biosciences, Gemini, Genentech, Gyroscope, Katalyst Surgical, Notal Vision, Novartis, Regeneron and Spark Therapeutics, and holds a patent with Katalyst Surgical.

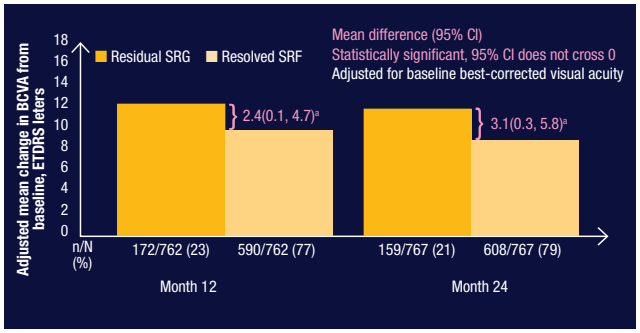

Figure 2. Eyes with residual subretinal fluid had significantly greater improvement in best-corrected visual acuity than eyes with resolved SRF. The presence of SRF and intraretinal fluid were evaluated independently. (ETDRS: Early Treatment Diabetic Retinopathy Study)

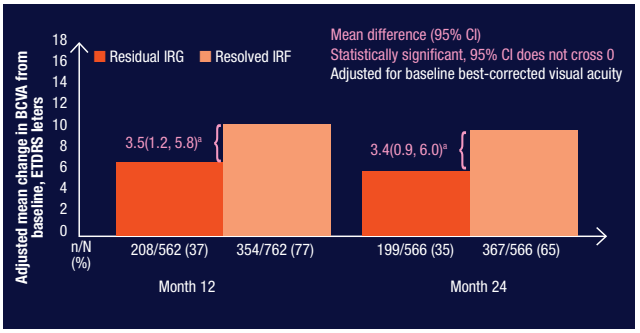

Figure 3. Eyes with residual intraretinal fluid had significantly less improvement in best-corrected visual acuity than eyes with resolved IRF. The presence of subretinal fluid and IRF were evaluated independently. (ETDRS: Early Treatment Diabetic Retinopathy Study).

Lessons from HARBOR post-hoc analysis

A post-hoc analysis of the HARBOR randomized clinical trial offers insight to this question.1 Of the 1,097 treatment-naïve patients with nAMD randomized in HARBOR, 917 met inclusion criteria of 24 months of available spectral-domain optical coherence images and either SRF and/or IRF present at baseline, screening or week one, and were pooled for an analysis of fluid and vision parameters. The primary outcome was fluid status and change in best-corrected visual acuity from baseline.

Importantly, fewer than 30 percent of eyes in the analysis population had residual SRF or IRF after 12 and 24 months of ranibizumab injected monthly or prn (*Figure 1*).

The post-hoc analysis also examined SRF and compared adjusted mean change in BCVA in eyes with residual SRF to eyes with resolved SRF at months 12 and 24 (*Figure 2*). Eyes with residual SRF had statistically better visual acuity outcomes than eyes with resolved SRF. In short, when looking at SRF, drier was not necessarily better.

In contrast, eyes with residual IRF had statistically worse visual acuity outcomes than eyes with resolved IRF at months 12 and 24 (*Figure 3*). In short, when looking at IRF, drier was definitely better.

A more nuanced view of fluid

It's important to note that in HARBOR, all eyes were treated monthly or PRN with the purpose of "drying the retina". Retinal fluid was not tolerated; rather, it was treated consistently.

However, some eyes with nAMD will never achieve complete resolution of fluid, even with treatment. Under these circumstances, the HARBOR post-hoc analysis demonstrated that eyes with persistent SRF see better than eyes that are dry, and eyes with persistent IRF see worse than eyes that are dry, suggesting a very complex relationship between retinal fluid and functional outcomes.

Bottom line

Given this HARBOR analysis and emerging analyses of other large data sets in nAMD, such as the LADDER trial, perhaps a more nuanced view of fluid status and visual acuity outcomes is warranted.

Editor's note: This article is based on a presentation Dr. Holekamp gave at the 37th annual meeting of the American Society of Retina Specialists July 27, 2019, in Chicago.

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Targeting a novel enzyme in GA

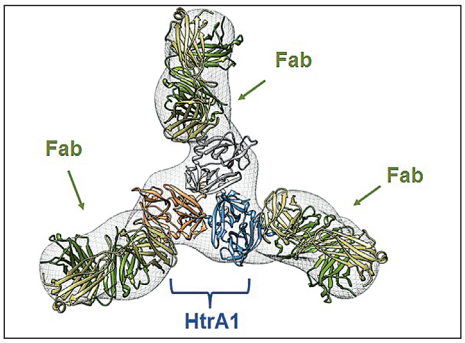
An investigative antibody aims to inhibit HtrA1 that contributes to progression of geographic atrophy. By Richard Mark Kirkner

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

The Phase I open-label trial in GA reported no ocular or systemic adverse events in the 28 patients dosed, and showed a potential for eight-week target inhibition at the 20-mg dose.

High-temperature requirement A1 (HtrA1) is an enzyme that may be implicated in the progression of age-related macular degeneration.[1] In 2017 Genentech applied for a patent on anti-HtrA1 antibodies,[2] and has pursued a clinical trial of RO7171009, an investigative intravitreal treatment that targets this novel pathway in geographic atrophy secondary to AMD.[3] At the Angiogenesis, Exudation and Degeneration 2020 meeting last month in Miami, principal investigator Vrinda Hershberger, MD, PhD, of Florida Eye Associates in Melbourne, reported on a Phase I trial in which anti-HtrA1 was well tolerated and showed pharmacodynamic assay results relating to drug activity in patients with GA.

HtrA1 is a trimeric serine protease that's widely expressed in the retina, and the ARMS2/HtrA1locus has a compelling genetic association with AMD. When targeted with the anti-HtrA1 antibody, a Fab of humanized monoclonal antibody, HtrA1 forms a cage-like inhibition complex, as the Genentech developers described.[1]



Three-dimensional reconstruction of the HtrA1_Cat–Fab94 complex's three active sites with the three bound Fab94 molecules in a propeller-like arrangement. The HtrA1_Cat protomers are gray, orange and blue; Fab94 heavy chain in green and light chain in dark yellow. (Used with permission: *Biochemical Journal*)

The Phase I open-label trial in GA reported no ocular or systemic adverse events in the 28 patients dosed, and showed a potential for eight-week target inhibition at the maximum 20-mg dose, Dr. Hershberger reported at the conference. Now the Phase II GALLEGO trial of 285 patients with GA is enrolling.[4] It has a primary completion date of March 2022. Here, Dr. Hershberger answers questions about the clinical trials and describes how the drug candidate works.

Q Describe the mechanism of action of anti-HtrA1 in your own words.

A Let's start with the therapeutic hypothesis for targeting HtrA1. HtrA1 induces breakdown and elimination of the extracellular matrix protein, resulting in atrophy of the photoreceptors, retinal pigment epithelium and Bruch membrane choroid. HtrA1 may also affect the visual cycle, as well as the stability of proteins required for photoreceptor and RPE cell survival.

We also know that in the human retina, HtrA1 expression is increased in the area perilesional to the GA. Mice overexpressing human HtrA1 have thinner retinas and decreased electroretinography activity compared to wild-type mice. So, Genentech has developed the anti-HtrA1 antigen-binding fragment that's a potent inhibitor of HtrA1 activity, with the hypothesis that inhibiting HtRA1 may slow the progression of lesion growth in GA.

Q What's the significance of targeting ARMS2/HtrA1 loci?

A Human genetics highlights pathways important for AMD pathogenesis. Several genetic studies over the past 20 years have shown the ARMS2/HtrA1 locus is one of the strongest genetic factors for risk of advanced AMD. Furthermore,

the ARMS2/HtrA1 risk variants are associated with progression from intermediate to advanced AMD and with increased lesion growth rates in geographic atrophy.

Q What are the key findings from the Phase I open-label trial?

A The primary objectives of the study were to investigate the ocular and systemic safety and tolerability of anti-HtrA1 following single and multiple intravitreal doses. Another objective was to determine the maximum-tolerated dose of anti-HtrA1 administered as a single dose and as multiple intravitreal doses.

The study found that the intravitreal-administered anti-HtrA1 as single doses (ranging from 1 to 20 mg) as well as multiple doses of 20 mg administered every four weeks over 12 weeks were well-tolerated. The study found no dose-limiting toxicities, ocular serious adverse events or systemic or ocular AEs.

Q How did the trial evaluate the drug activity?

A This study design incorporated mandatory aqueous humor sampling. Not only did this allow for evaluation of drug concentration and elimination, but because of a novel enzyme-activity-based pharmacodynamic (PD) assay, the study was able to evaluate actual drug activity. The aqueous humor samples were analyzed for cleaved-DKK3, which is produced by cleavage of DKK3 by HTra1. In the presence of the anti-HTRA1 antibody, cleaved-DKK3 levels drop. Dose-dependent duration of reduction of cleaved-DKK3 was seen in the single-ascending-dose cohort, with the higher doses showing eight-week inhibition. Similar results were seen in the multiple dose cohort, demonstrating the direct ability to show downstream activity and duration of action of the drug.

Q How have those findings informed the Phase II trial design?

A Because we don't know how much HtrA1 inhibition is necessary to slow progression of GA, we wanted to test the maximum-tolerated dose in the Phase I study, which was 20 mg administered every four weeks for three months. However, because decreasing frequency of intravitreal injections is very important to patients, we also decided to test the 20-mg dose every eight weeks, which was informed by the PD biomarker data.

Q Are there any potential challenges with the Phase II trial?

A This trial is unique because it uses a three-month pre-screening period. We will collect baseline images three months before the actual screening date so we can assess the actual growth rate of GA. That information will be used to stratify patients to four- or eight-week treatment arms. The prescreening increases the length of the trial. The primary endpoint is change in GA area from baseline at 72 weeks. RS

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Pearls for complex diabetic TRD repair

(Continued from page 15)

plaques around breaks combined with proliferative vitreoretinopathy and vitreous-base contraction, consider a large (90- to 180-degree) retinectomy and a scleral buckle to relieve traction successfully.

At the end of the case, whether or not we find a break, we use a long-acting gas tamponade (C3F8 14 to 16%) with two to three weeks of face-down positioning. We reserve silicone oil only for cases with a large inferior retinectomy. This avoids recurrent vitreous hemorrhage mixing with oil, and long-term oil complications.

Bottom line

We've had excellent results with this approach, with a 98.6 percent single surgery reattachment rate in 69 consecutive diabetic TRD cases.[1] The long-acting gas tamponade can protect from unseen breaks or those that develop from hot laser or stretching as residual membranes regress.

In one recent patient, we noted a new hole at postop week three as the C3F8 bubble was shrinking. The hole was located within the detached area and eluded notice intraoperatively. In this case, thankfully, the gas and positioning served to tamponade the new hole while subretinal fluid was reabsorbed in that area postoperatively. This helped to prevent any subretinal fluid around this inferior break which was subsequently easily barricaded in the office (*Figure B, page 15*). RS

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New day for extended ophthalmoscopy

New rules and codes apply starting this year. The requirements are tighter and the reimbursements lower.

By Ellen R. Adams, MBA

The CPT codes for extended ophthalmoscopy, initial (92225) and subsequent (92226), were retired at the start of the year, having been replaced by two new codes. Although there are some similarities between them, changes in definitions for the new codes can lead to coding errors if the distinctions are overlooked.

THE NEW CODES

First, let's look at 92201, defined as:

Ophthalmoscopy, extended, with retinal drawing and scleral depression of peripheral retinal disease (e.g., for retinal tear, retinal detachment, retinal tumor) with interpretation and report, unilateral or bilateral.[1]

The first issue to recognize is that this code doesn't state "initial" or "subsequent." The second significant issue is that this code is "unilateral or bilateral." In other words, you'll receive payment for one service whether you examine one or two eyes. Significantly, 92201 is a peripheral retinal drawing code and requires scleral depression.

The second new code is 92202 and it's distinctly different from 92201:

Ophthalmoscopy, extended, with drawing of optic nerve or macula (e.g., for glaucoma, macular pathology, tumor) with interpretation and report, unilateral or bilateral.[1]

As with 92201, this code isn't "initial" or "subsequent," and it has one payment whether one or both eyes require a drawing. However, it doesn't require scleral depression.

Policy considerations

Payer policies will vary somewhat for these two codes. Generally, they'll require a "large, scaled" drawing. Some policies specify the diameter of the drawing as three to four inches. Some require color. All payers require the drawing be labeled and include an interpretation and report. In addition, the method of examination (dilated, supine and/or type of lens used) needs to be documented.

A review of payer policies reveals covered diagnoses for the new codes. One may assume 92201 will be covered for diseases affecting the peripheral retina, and 92202 will cover macular and optic nerve conditions. Because there's some overlap, you may see diagnoses that are, at first blush, peripheral but are covered for 92202. On further thought, you'll note that diseases such as diabetic retinopathy may have peripheral as well as macular manifestations.

Another word of caution: If you repeatedly use a "peripheral" diagnosis for 92202 or an optic nerve diagnosis for 92201, payers may revise policies to narrow covered diagnoses. So use care and thought in selecting the appropriate diagnoses.

Multiple National Correct Coding Initiative (NCCI) edits apply to these codes. Significantly, CPT specifies 92201 and 92202 can't be billed with each other, and neither can be billed with fundus photography (92250). NCCI agrees. The codes are also bundled under NCCI with intravitreal injection (67028) and most retinal surgeries.

Although 92201 and 92202 are bundled with 92250, the new codes don't have NCCI edits with scanning computerized ophthalmic diagnostic imaging/optical coherence tomography (92133/92134) or fluorescein angiography (92235). That may change in the future.

Payment rates

Unfortunately, the fee schedule is lower than the retired codes: 92225 and 92226 had a national average payment rate of $28 and $26 respectively; the new codes are valued at $26 (92201) and $16 (92202).[2]

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

Bio

Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

Other considerations

Can you bill both 92201 and 92202? Perhaps. Patients who have multiple diseases and require both a peripheral and fundus or optic nerve drawing will require meticulous documentation supporting medical necessity for both 92201 and 92202. If you decide both tests are medically necessary, you'll be required to submit separate drawings, interpretations and diagnoses with the claim for payment.

The second test may be submitted with the XS modifier, "Separate Structure." However, with the exception of Medicare, payers rarely recognize this modifier and denial is likely. And if the documentation is weak, an audit will result in payment retraction and with the potential to expose you to a wider audit, so use caution.

Strategies

It's important to first be sure your charge capture and electronic medical record are configured to accept the new CPT codes. Next, a careful review of the drawing templates is needed. You should have different templates for 92201 and 92202.

And finally, Medicare payer policies require careful review to be sure drawing requirements, covered diagnoses and NCCI edits are fully understood. Understand payer policies before you submit a claim.

Information on NCCI edits is available on the Centers for Medicare and Medicaid Services website (www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd). NCCI edits also are available from Medicare carriers and a few commercial vendors. RS

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Gene therapy and editing for retina: A primer

(Continued from page 24)

although it has only shown success in animal studies.

However, given the bacterial origin of CRISPR systems and the permanent impact of genome editing, potential host immune responses and off-target effects require thorough investigation before human trials commence. RS

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Department Editor *Kari Rasmussen*

How to lock in staff in a tough job market

With unemployment at an all-time low, these seven steps will help you get and keep the right people.

Kari Rasmussen

Jane Palmer

Whether you are a single doctor managing all aspects of your practice or a practice administrator managing 150 employees your challenge to recruit and retain a well-trained, compassionate and loyal team is the same.

Finding the right people is even more difficult today with unemployment rates at an all-time low, so here I'll provide some insight for retaining and developing your team in these difficult times. Here are seven strategies to help you achieve low staff turnover.

1. Share your mission

That is, make your practice mission statement known to all staff and share it with new hires in the interview process so they understand the goals of the practice. Have a comprehensive personnel policy, provide quality management and employee training. This helps to ensure a professional atmosphere that fosters teamwork and employee growth.

2. Hire selectively

This goes beyond finding the right skills; new hires should also fit your practice's culture. Determine the key traits you desire for each position in your practice and seek candidates that best match your needs. If you compromise, it may cost you in the long run with poor staff morale, performance issues and other personnel problems.

3. Offer competitive salary and benefits

This is key for keeping long-term employees. Regional salary surveys can tell you how your compensation and benefits compare to similar positions in your area. Many clinicians think that paying a lower wage ultimately saves them money, but in my experience, you get what you pay for.

4. Offer a healthy work-life balance

This includes creating flexible work schedules or extra time off.

5. Help your employees get ahead

For staff who want career advancement, provide leadership and continuing-education opportunities. Depending on your practice size, have team lead positions for staff to champion various duties. Resources outside the practice can be very effective in achieving this as well. Lean on our local or state ophthalmology organizations as well as professional organizations such as the American Society of Retina Specialists and American Academy of Ophthalmology for their skill-development tools.

6. Hear them out

Make staff feel comfortable expressing ideas, sharing feedback and brainstorming to solve issues. This will cultivate a work environment that nurtures team building.

7. Show them you appreciate them

Give confirmation for work well done. Let staff know their talents are appreciated. Perhaps recognize staff on birthdays or hiring date anniversaries to remind them of their value. Office outings such as occasional picnics or bowling nights can promote team-building and camaraderie. Face-to-face appreciation goes a long way.

Step back and think about it

All of these strategies require dedicating resources that can be in short supply when trying to manage the day-to-day operations of a busy retina practice. With employees being our most important commodity, we must step back and consider how to integrate these ideas to protect our ability to provide exceptional service to our patients, our practice and our providers. RS

Bios

Ms. Rasmussen is chief operating officer of Rocky Mountain Retina Consultants, Salt Lake City, Utah.

Ms. Palmer is practice administrator at Pennsylvania Retina Specialists in Camp Hill.

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

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

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

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

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

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

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

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

(continued)

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

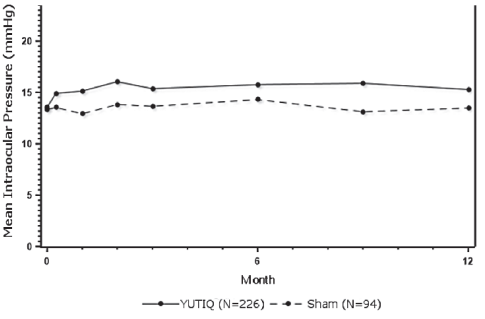
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

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

Table 2: Summary of Elevated IOP Related Adverse Reactions

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

Figure 1: Mean IOP During the Studies



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

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

Discover continuous calm in uveitis

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg:

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

For more information, visit

J code: J7314

YUTIQ.com

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

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

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

EyePoint® PHARMACEUTICALS

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