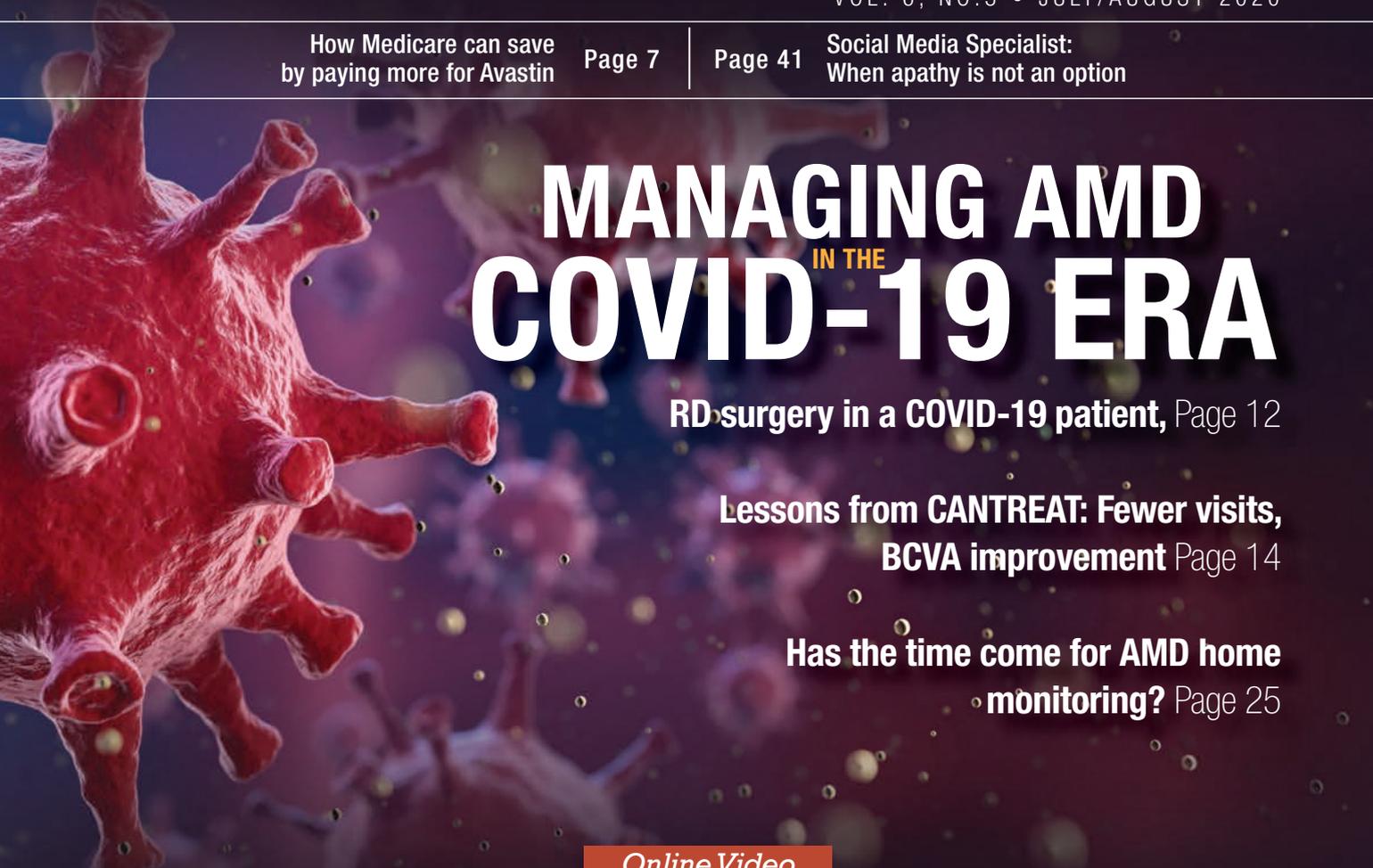


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Diversity and a vaccine

There will always be forces among us—in our practices, in our institutions, in our countries and beyond—that will try to divide and antagonize one against another. We need to recognize these forces, call them out by name and, wherever possible, seek common ground to build on a foundation of mutual respect.

In their purest forms, science and the pursuit of improving human quality of life for all can be beacons of hope that manifest the potential good in humanity. The ongoing global cooperative effort to generate a vaccine against SARS-CoV-2 (as our current coronavirus is formally known) appears to be an example of such a worthwhile endeavor.

On January 10, the sequence of the virus was released to the public. Approximately 62 days later the first vaccine candidate was injected into a volunteer's arm as part of a Phase I safety study. By the end of May, more than 170 vaccine candidates were under development, representing an incredible range of approaches from the traditional to very novel.

This timeline and the diversity of approaches are unprecedented. No vaccine has ever been developed to commercialization in less than about four years, a feat achieved for mumps in the 1960s. Nevertheless, data-based commentary from scientists have sounded cautiously optimistic that a vaccine may be available later this year or early next.

While playing out on a fraction of the scale, innovation in retina can and should be a place where collaboration and diversity—of background, experiences and perspectives—are similarly welcomed and intentionally cultivated. Moving ideas into reality through preclinical studies, early then late phase clinical trials and ultimately to widespread clinical adoption is a colossal task, requiring years of effort and innumerable skill sets.

In these pages some ongoing innovations in retina, such as defining new biomarkers correlated with genetic loci in age-related degeneration by Johanna Seddon, MD, ScM, (page 34) and the development of home optical coherence tomography capabilities by Judy E. Kim, MD, (page 25) are described.

As the world prepares for Phase III vaccine trials to ultimately end COVID-19, there will be more controversies—for example, in the ethical debate surrounding a new breed of more efficient trials, i.e., human challenge studies.

As we forge ahead globally and more specifically within retina, we must prioritize the essential value of real diversity. The different perspectives that come from disparate experiences are fundamental to innovation. 

A PUBLICATION BY RETINA

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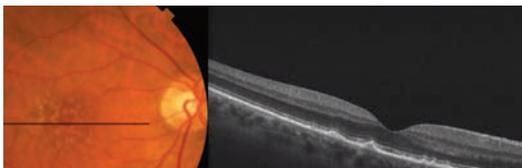
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When apathy is not an option

By David R.P. Almeida, MD, MBA, PhD

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***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 intraocular 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

Intraocular Injection-related Effects: Intraocular 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 intraocular 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 intraocular implant) 0.18 mg full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. October 2018. **2.** EyePoint Pharmaceuticals Receives FDA Approval of YUTIQ™ (fluocinolone acetonide intraocular 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-intraocular-implant-0-18-mg.html>. Accessed February 7, 2020. **3.** Data on file.

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



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2/2020
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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

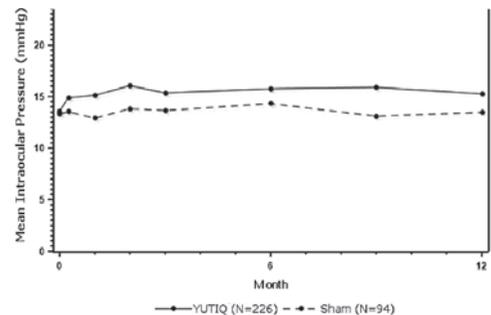
Ocular		
ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham Injection (N=94 Eyes) n (%)
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		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

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How Medicare can save by paying more for Avastin

If Medicare increased its reimbursement for intravitreal bevacizumab (Avastin, Roche/Genentech) to equal what retina specialists get for a more costly competitor, it would actually reduce payer and patient costs by more than \$500 million annually, according to a cost-analysis study published in the journal *Ophthalmology*.¹

The idea of increasing reimbursement for a lower-cost medication is controversial. The study drew on ISIS Registry data of 2.6 million intravitreal injections for Medicare fee-for-service patients in 2018. The estimates are calculated on Medicare costs of \$1,559.76 for aflibercept and ranibizumab 0.5 mg (Eylea, Regeneron Pharmaceuticals, and Lucentis, Roche/Genentech) and \$855.91 for Lucentis 0.3 mg, with patients responsible for 21.2 percent of the average sales price for these drugs, and \$70.56 for bevacizumab, with the patient covering 20 percent.

The study calculated that the total physician payment above cost for Eylea is \$80.78 vs. about \$25 for Avastin. Medicare would actually cut costs by adding that \$80.78 to the reimbursement for Avastin, the study states.

The study notes that Medicare Part B spends more than \$3.5 billion annually on anti-VEGF drugs and the volume of intravitreal injections has been increasing 6 to 8 percent a year over the past five years.

Lead study author David B. Glasser, MD, of Johns Hopkins University and the American Academy of Ophthalmology's secretary for federal affairs, tells *Retina Specialist* that now that the paper has been published, the next step is to take this data back to Medicare administrative contractors (MACs) to convince them to increase payment for Avastin.

As it is, the study found that Avastin injections have been decreasing steadily, from more than 70 percent in 2012 to 55 percent in 2013 to 45 percent in 2018.

Of course, the cost equation for Avastin changed more so last summer when United States Pharmacopeia issued stricter requirements for syringes, driving up costs specialty pharmacies passed onto physicians. "The cost went up last summer and



David B. Glasser, MD

the reimbursement did not," Dr. Glasser says. "Practices who were sort of limping along and still giving Avastin at a break-even or maybe a very slight loss were now underwater and stopped using it." By 2019, IRIS data showed, Avastin accounted for a little more than one-third of all Medicare fee-for-

service intravitreal injections.

He notes that many retina specialists have stuck with Avastin "despite the fact that they were making very little money or possibly even losing money on each injection, and the reason they did it was because they thought it was the right thing for the patient."

But does that mean there's enough upside demand for Avastin to justify Medicare increasing the physician fee for it? Dr. Glasser and colleagues found a study of a regional health plan that reported a 9-percent increase in Avastin use by increasing its reimbursement to be competitive with Eylea and Lucentis.² "Do we think there's anything fundamen-

IN BRIEF

Iveric Bio has dosed the first patient in the GATHER 2 Phase III clinical trial of the novel complement C5 inhibitor avacincaptad pegol (**Zimura**) for treatment of geographic atrophy secondary to age-related macular degeneration. The company previously announced 18-month results from the first Phase III trial (OPH2003) of Zimura that showed 28.11 percent and 30 percent mean rates of reduction in GA growth for the 2- and 4-mg groups, respectively.

"No merit" is how **Regeneron Pharmaceuticals** characterizes the Department of Justice civil complaint that it paid tens of millions of dollars in kickbacks through a charitable foundation. The U.S. Attorney's office in Boston filed two civil counts alleging Regeneron violated the False Claims Act by directing its contributions to the Chronic Disease Fund only went toward Medicare co-pays for patients using Eylea. Regeneron calls the suit "misguided" and says it has "fully cooperated with the government's investigation and will vigorously defend" its case.

RETINA UPDATE

tally different in Medicare fee for service?” Dr. Glasser says. “Probably not. In fact, there might even be more suppression of Avastin use based on the poor reimbursement when you consider that some MACs are paying as little as \$50 for the drug.”

The study modeled Medicare savings on 5-, 7.5- and 10-percent increases in Avastin market share. The model breaks even with a 0.74-

percent increase. The 10-percent increase would yield \$468 million in Part B savings and a \$119 million reduction in patient co-pays annually.

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New publisher at the helm

Michael Hoster, a 13-year veteran of Jobson Medical Information, publisher of *Retina Specialist Magazine*, has been named publisher of the Review Group of publications and services.

Besides *Retina Specialist*, the Review Group includes *Review of Ophthalmology*, *Review of Optometry*, *Review of Cornea and Contact Lenses* and affiliated websites, e-newsletters and other digital media.

Mr. Hoster assumes the position previously held by James Henne, who's retiring after having served as publisher since 2014. Mr. Hoster has spent his entire professional career at Jobson, first as associate editor and then managing editor of *Review of Optometry* and then joined *Review's* sales team in 2015.

Mr. Henne joined Jobson as a sales manager for the *Reviews* in the late 1990s after a long career as a publisher and account executive at Chilton Company, previous owner of the *Reviews*. 



James Henne



Michael Hoster

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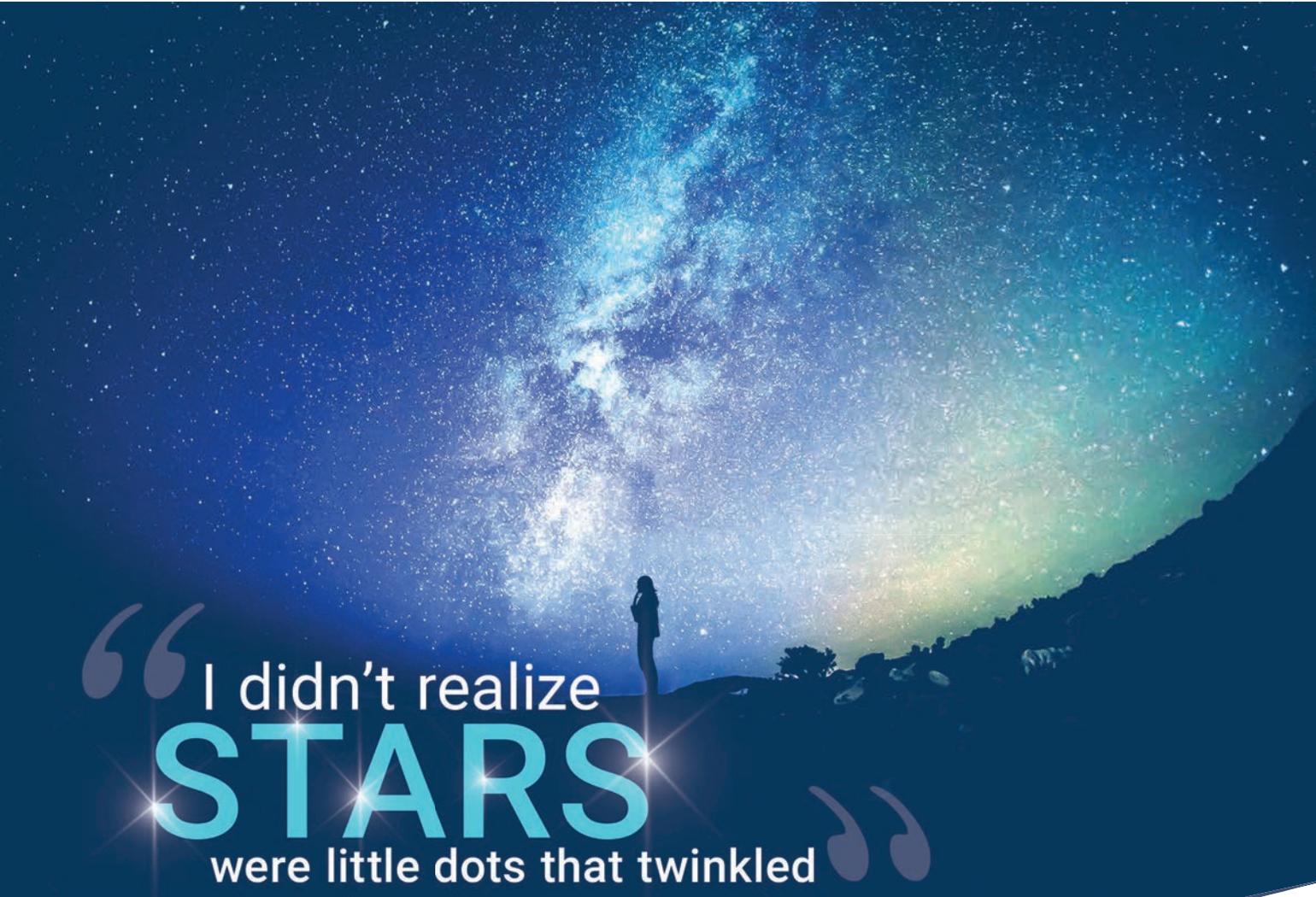
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A novel approach for sutureless closure

‘Scleral acupuncture’ is one option for sutureless repair of a leaking sclerotomy.

By *Parnian Arjmand, MD, MSc, FRCSC*
Tina Felfeli, MD, and
Efrem D. Mandelcorn, MD, FRCSC



Parnian Arjmand, MD, MSc, FRCSC



Tina Felfeli, MD

Despite the advent of microincision vitrectomy surgery, up to 38 percent of sclerotomy sites are sutured to achieve proper wound closure after 23- and 25-ga. pars plana vitrectomy.¹⁻⁷ Risk factors for a leaking sclerotomy include high myopia, thin sclera, multiple instrument exchanges, retinal detachment repair, prior history of PPV, extended peripheral vitrectomy and combined phacovitrectomy.^{1,2}

Most surgeons opt to suture leaking sclerotomy sites to minimize the risks of postoperative hypotony and endophthalmitis. Others may suture nonleaking sclerotomies to mitigate the chance of postoperative leaks from blinking or eye rubbing to ensure a complete fill with the tamponade agent of choice (air, gas or oil). Nevertheless, disadvantages of suturing wounds include increased operating time, postoperative patient discomfort, episcleritis, pyogenic granuloma formation and surgically induced astigmatism.

Several alternative techniques to suturing sclerotomy wounds have been described, including scleral wound hydration, adhesive glue, conjunctival cautery or the use of a lightbulb/fine needle to guide removal of the cannula and apply scleral pressure.^{1,8}

All of these techniques have associated limitations. Identifying the edges of the sclerotomy wound for hydration is not always possible when conjunctival chemosis or subconjunctival hemorrhage is present. Glue is time-consuming and can be very uncomfortable for the patient postoperatively. Cautery has been associated with scarring and inflammation with variable efficacy.

Scleral needling technique

We describe a novel scleral needling (SN), or “scleral acupuncture”, technique to achieve sutureless closure of leaking sclerotomy sites following 23- or 25-ga. PPV.¹

In this technique, following the removal

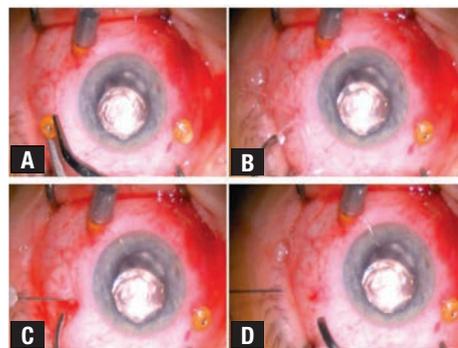


Figure 1. After air-fluid exchange, (A) the trocar cannula is removed and (B) balanced salt solution is dripped over the sclerotomy site for visualization of air bubbles to detect a leak. A 30-ga. needle (C) is inserted perpendicular to and full-thickness through the sclera adjacent the opening (C) and then (D) immediately removed, and sclerotomy closure is confirmed. (Published with permission Retina, Wolters Kluwer)

of the trocar cannula, a 30-ga. needle attached to a closed 1-mL syringe is inserted perpendicularly within the sclerotomy wound bed and quickly removed. Subsequently, a 19-ga. cannula is used to apply gentle pressure over the sclerotomy site for three seconds (*Figure 1*). Any residual leakage is then detected with basic salt solution irrigation and the needling is repeated if necessary (*Video*).

We performed a retrospective comparison of 203 eyes undergoing PPV including 105 eyes prior to the introduction of scleral needling (pre-SN group) and 98 eyes following the integration of scleral needling in our practice (post-SN). Our results suggested that 39 percent of eyes in the pre-SN

View the Video



Drs. Arjmand, Felfeli and Mandelcorn demonstrate key steps in the sutureless needling procedure. Available at: https://bit.ly/RetSpecMag_07202001

[ly/RetSpecMag_07202001](https://bit.ly/RetSpecMag_07202001)

Bios

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DISCLOSURES: The authors have no relevant relationships to disclose.

group required suturing vs. only 2 percent of eyes in the post-SN group.

Most importantly, we found no significant difference in rates of hypotony or intraocular pressure between either cohort on days 1 to 20 postoperatively. In fact, SN was associated with a significantly higher incidence of subconjunctival hemorrhage and better visual acuity postoperatively compared to eyes in the pre-SN cohort.

How does scleral needling work?

Although the exact mechanism of wound closure with this technique isn't clear, two mechanisms have been proposed. Some speculate that SN draws vitreous to the inner os of the sclerotomy wound, plugging it. We've demonstrated this using vitrectomized cadaveric eyes with an endoscope illumination system.

Using intravitreal triamcinolone, we observed that needling draws vitreous strands to the needle-entry site (Figure 2). Secondly, scleral needling may create a siphoning effect that draws fluid or air to the new entry site away from the main wound, resulting in wound closure.¹ Another possibility is that a sudden drop in intravitreal pressure relative to the pressure outside the eye created by the exiting needle from the sclera may close the wound (Figure 3).⁹⁻¹¹

Technical pearls

At the end of the case, we often do at least a partial fluid-air exchange to help identify and air leaking from the corneal wounds at the end of the case. We prefer to use a 30- or 27-ga. needle, both of which work effectively. Our usual routine is to partially remove the trocar and then pre-place a 30-ga. needle attached to an empty TB-syringe perpendicular to the sclera just adjacent to the trocar in the bed of the scleral wound. As we remove the trocar, the needle is dipped into the vitreous cavity, about halfway down the needle tip and then removed entirely.

A blunt 19-ga. cannula, usually attached to the irrigating BSS bottle, is then used to firmly press on the scleral wound bed. A few

drops of BSS are used to inspect the wound for any air leaks, and if we note any, we needle the sclera again and use cannula to press on the wound.

Some cases can require up to five scleral needles, but about 98 percent of the wounds stop leaking and close completely. This technique works very well in both air-filled and silicone-filled eyes.

Bottom line

Scleral needling is a simple, safe, and effective technique to achieve wound closure following 23- and 25-ga. PPV. 

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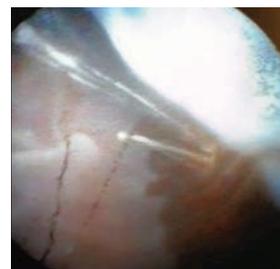


Figure 2. Intraoperative triamcinolone allows for visualization as the needling draws vitreous strands to the needle-entry site.

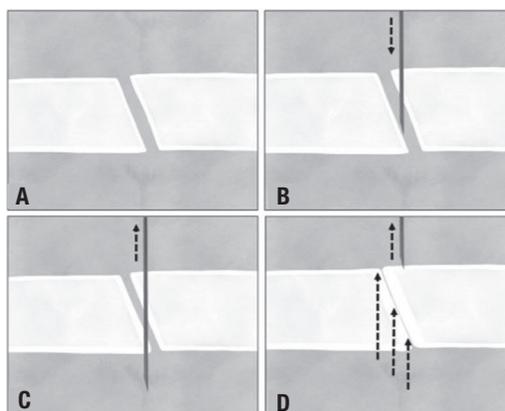


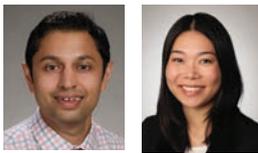
Figure 3. Mechanisms by which scleral needling may result in wound closure are by creating a siphoning effect that draws fluid or air to the new entry site away from the main wound; or a sudden drop in intravitreal pressure relative to pressure outside the eye as the needle exits the sclera (A through D). (Published with permission Retina, Wolters Kluwer)



RD surgery in a COVID-19-positive patient

Routine repair of a retinal detachment becomes complex during a global pandemic.

By Debarshi Mustafi, MD, PhD, Elysse Tom, MD, and Aaron Y. Lee, MD, MSCI



Debarshi Mustafi, MD, PhD

Elysse Tom, MD



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CCOVID-19 has had a profound impact on our practice as retina specialists. On January 20, Washington state, where we practice, confirmed the first COVID-19 case in the United States. Seattle rapidly became the country's first hot spot and where the community transmission of the disease was first noted.¹

Patients with COVID-19 have complained of visual impairment,² with recent reports of subtle retinal findings without associated vision changes.³

As retina specialists, we have a unique risk of exposure because we come into close face-to-face proximity with our patients, particularly during intravitreal injections, laser procedures and even basic slit lamp examinations. As ophthalmologists practicing in one of the first epicenters of the country, we quickly reduced the volume of clinic visits and restricted patient encounters to urgent and emergent visits to slow the spread of the virus and preserve resources.

While we attempted to limit potential interactions with COVID-19 positive patients in clinics, we were also responsible for seeing patients who came in through the emergency department with acute eye symptoms who needed to be managed with COVID-19 precautions. Due to the nature of our specialty, many patients have eye conditions that require urgent care. Here we discuss the surgical evaluation and management of one of our practice's first COVID-19-positive patients.

Relying on ED personnel

In April, a middle-aged man with a history of recent mild respiratory symptoms and known exposure to family members positive for COVID-19 presented to the Harborview Medical Center emergency department with a gradual decrease in vision in one eye. The patient was first tested for COVID-19 using a reverse transcription

polymerase chain reaction (RT-PCR) of a sample obtained by nasopharyngeal swab. The test was positive and the patient was placed in a negative-pressure room for ophthalmic examination.

He did not require any supportive therapy for his respiratory symptoms. We quickly determined that a powered air-purifying respirator (PAPR) could not be used to carry out an indirect dilated fundus exam and that an N95 with a face mask was necessary.

Fortunately, our ED had well-trained personnel to help us don and doff protective gear so we could safely enter and exit the room to examine the patient. The patient was diagnosed with a macula-involving retinal detachment in the symptomatic eye.

Given that this patient had a single superior retinal tear in a phakic eye, we offered



Figure 1. Drs. Lee and Mustafi prep for surgery. Additional personal protective equipment for the case included N95 masks underneath surgical masks fitted with face shields and isolation gowns over their surgical scrubs.

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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. Lee is an assistant professor of ophthalmology specializing in vitreoretinal surgery, Dr. Mustafi is a retina fellow and Dr. Tom a resident.

him a pneumatic retinopexy while noting that this technique would mean he would need closer postoperative follow-up with possible later interventions such as laser, which could be challenging to coordinate because of his COVID-19 status. After we had a complete discussion of pneumatic retinopexy vs. pars plana vitrectomy, he elected to proceed with a PPV for the RD repair.

Planning the operation

We planned the operation for a few days later, and we discovered the challenges and intricacies of scheduling a COVID-19 patient for outpatient surgery. As we soon learned, this was the first COVID-19-positive patient to have outpatient surgery at Harborview Medical Center. After extensive discussion with the perioperative staff, anesthesiologists and our surgical team, we developed a plan to keep all involved parties, including the ill patient, the other patients scheduled for eye surgery that day and all surgical staff, as safe as possible.

On the morning of the surgery, the patient was again placed in a negative-pressure room in the preoperative area, and trained personnel helped us don and doff before we entered and after we exited the room. Another interesting twist was that the patient's spouse also tested positive for COVID-19 and had to be placed in an isolated waiting room for the duration of the case.

Because using PAPRs would have hindered our ability to operate at the microscope, we wore N95 masks with an overlying eye-shield for added protection. While we considered avoiding intubation to decrease the risk of viral-particle aerosolization and performing the case under monitored anesthesia care, the patient strongly favored general anesthesia, which was performed with only the anesthesiologist (who was able to wear a PAPR) in the operating room.

Once the patient was induced and fully

Confirmed COVID-19 case counts in Washington state

• Confirmed cases • Data are incomplete for the most recent dates

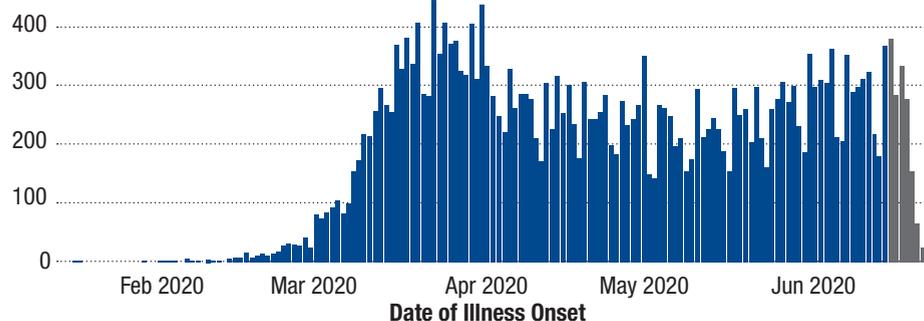


Figure 2. This epidemiologic curve shows the progression of the COVID-19 outbreak in Washington state by cases, including hospitalizations and deaths, over time. Data are from the Washington State Department of Health.

intubated to avoid exposure to aerosolized virus particles, we entered the OR. After we completed the surgery, we promptly exited the room before the patient was extubated, again to decrease the risk of exposure. The patient was then allowed to recover initially and wake up in the OR for a period of time before being transported back to a negative-pressure room for recovery.

Postoperative care

On post-op day-one and week-one visits, we examined the patient in a negative-pressure room in our clinic. We asked the patient to arrive early before other patients. To avoid exposure and contamination, we organized a station outside the room to don and doff as we had done previously in the ED and OR.

By the one-month visit, the patient had fully recovered from his respiratory symptoms. His retina was attached, and his vision had improved from counting fingers preoperatively to 20/50 with correction. The patient still had a gas tamponade agent in his eye, and we will see him again in a month. Overall, he is healing well after a safe and successful surgical intervention.

Three key lessons in COVID-19 care

This case highlights three important lessons regarding the technical challenges, resources and significance of caring for patients during a pandemic:

(Continued on page 16)

Managing nAMD in the COVID-19 era

Lessons from CANTREAT: fewer visits, BCVA improvement

Level 1 evidence now supports treat-and-extend vs. monthly intervals for anti-VEGF treatment of neovascular age-related macular degeneration.

By Parnian Arjmand, MD, MSc, FRCSC, and Peter J. Kertes, MD, FRCSC



Parnian Arjmand, MD, MSc, FRCSC



Peter J. Kertes, MD, FRCSC

Take-home points

- » CANTREAT is the largest Canadian randomized, open-label, non-inferiority, multicenter trial comparing two treatment regimens with ranibizumab for patients with neovascular age-related macular degeneration.
- » At two years, visual-acuity outcomes in the treat-and-extend (T&E) group were no worse than the once monthly (OM) group.
- » On average, T&E patients had 17.6 visits/injections over two years vs. 23.5 in the OM group.
- » T&E can achieve clinically meaningful improvement in best-corrected visual acuity with fewer visits/injections.

Bios

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Disclosures: Dr. Kertes has received research funding from Bayer, Allergan, Novartis and Roche; fellowship funding from Novartis and Bayer; has sat on advisory boards for Allergan, Novartis, Alcon, and Bayer; sits on the scientific advisory board for Novartis; and owns stock in Arctic Dx.

Dr. Arjmand has no relationships to disclose.

Neovascular age-related macular degeneration is a devastating cause of vision loss, especially in developed nations with an aging population. Although no definitive “cure” exists, anti-VEGF agents have revolutionized the disease outlook for our patients. Yet, many challenges persist. They’ve become more acute during the COVID-19 pandemic.

The burden of frequent visits and injections as well as treatment cost are major hurdles to timely, consistent care. To overcome them, some retina specialists follow a *pro re nata* and/or a treat-and-extend (T&E) strategy. The ultimate goal of these strategies is multi-faceted:

- to minimize disease activity;
- maintain or improve visual acuity; and
- minimize the number of injections.

Here, we report on the Canadian Treat-and-Extend Analysis Trial with Ranibizumab (CANTREAT) that provides evidence supporting less frequent injections, which can be valuable as we try to minimize patient visits during the pandemic.

Goal of CANTREAT

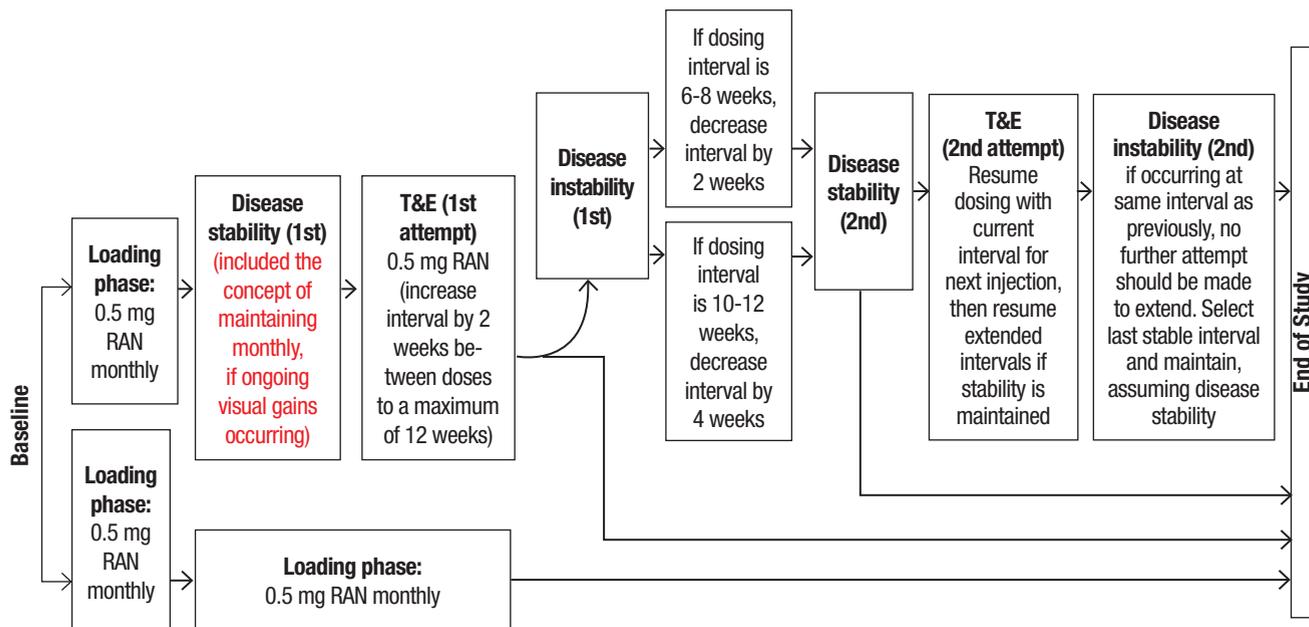
CANTREAT is a two-year randomized non-inferiority trial designed to compare the efficacy of administering ranibizumab (Lucentis, Novartis in Canada; Roche/Genentech) in a once-monthly (OM) vs. T&E approach across 27 Canadian centers.^{1,2}

Only two other trials, TREX and TREND, have prospectively compared the two regimens. However, TREX registered only 60 patients and had many missing data-points after two years. TREND did not continue beyond one year.^{3,4}

Two-year CANTREAT data

After two years, the Canadian Treat-and-Extend Analysis Trial with Ranibizumab yielded these two key findings:

- Mean improvement of 6.8 and 6 letters in the treat-and-extend and monthly arms ($p=0.21$), respectively
- Average number of injections at month 24 was 17.7 vs 23.7 for T&E and monthly arms ($p<0.001$), respectively.



CANTREAT randomized treatment-naïve patients to monthly or T&E treatment following an initial loading phase of three consecutive monthly intravitreal ranibizumab 0.5 mg injections (Figure 1). At baseline, all patients had a standard ophthalmic examination, Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity measurements and optical coherence tomography. OM patients also had monthly exams along with ETDRS BCVA measurements and OCT testing every three months. T&E patients received all diagnostic testing at each clinic visit. All patients had intravenous fluorescein angiography at baseline and at weeks 52 and 104

A total of 580 patients were enrolled (T&E=287, OM=293), approximately 80 percent of whom completed the 24-month follow-up. Primary outcomes were to determine whether mean change in BCVA from baseline to month 12 with T&E was non-inferior to monthly treatment and the number of injections it took to achieve those outcomes. Secondary outcomes were:

- Duration of treatment-free intervals.
- Percent of patients with a gain/loss of ≥ 5 , ≥ 10 , ≥ 15 ETDRS letters from baseline at 12 and 24 months.
- Mean change in BCVA at 24 vs. three months.
- Mean change in BCVA from baseline to month 24.
- Number of injections from baseline to month 24.

- Number of injections at months 12 and 24.

Compared with PRN dosing

Other than the TREX and TREND studies, the CANTREAT results can also be compared with PRN dosing in two other large clinical trials, CATT⁵ and IVAN.⁶ These studies reported PRN dosing to be no worse compared to monthly treatment, with a fewer number of injections through year two in the CATT trial in the PRN group. Similarly, HARBOR⁷ demonstrated that PRN dosing of ranibizumab could achieve clinically meaningful BCVA improvements, even though it failed to meet non-inferiority endpoints compared to monthly injections.

While many of us have been treating patients on a T&E regimen, CANTREAT provides Level 1 evidence for non-inferiority of this approach to monthly injections. At month 24, 73.7 percent of patients in CANTREAT were able to extend the treatment interval to eight or more weeks and 43.1 percent to 12 weeks. Certainly, the significantly fewer number of injections T&E management affords minimizes the burden and cost of care without compromising VA outcomes.

Tailoring treatment to patient needs

It should be emphasized that a T&E approach is tailored to every patient's needs. While some patients remain stable on a 12-week or longer injection interval, a signifi-

Figure 1. The treat-and-extend protocol in the Canadian Treat-and-Extend Analysis Trial with Ranibizumab (CANTREAT). (Published with permission from Kertes et al. Canadian Treat and Extend Trial with Ranibizumab in Patients with nAMD: CANTREAT Study 24-month Results. COS 2019)

cant proportion need monthly injections. These patients may still have good visual outcomes and should not be considered treatment failures. The goal is to stay ahead of disease activity and carefully increase intervals but only when it's possible and reasonable.

We should note that many CANTREAT patients whom we could not extend beyond six weeks (i.e., 26.2 percent by 24 months) ultimately did very well in terms of VA outcomes. In fact, BCVA improvement was similar between this cohort and those extended up to 12 weeks. We didn't find any correlation with interval extension and baseline characteristics such as age, central retinal thickness and subretinal fluid.

In CANTREAT, we didn't tolerate any subretinal fluid when deciding on interval extension. However, with current new evidence suggesting subretinal fluid can be tolerated without compromising outcomes,⁸ it's plausible that these patients could tolerate longer treatment intervals.

Tailoring treatment to patient needs also means keeping in mind the patient's comfort with more frequent injections, travel distance and level of understanding regarding the T&E philosophy. It's important to keep in mind that visual outcomes, not treatment interval or OCT findings, determine treatment success.

A cohort of CANTREAT patients have also been extended to three years. The three-year data have helped us understand long-term outcomes of nAMD patients treated with the T&E regimen in terms of VA, number of injections, geographic atrophy, intraocular pressure and characteristics that may help identify who may require fewer or more injections. ^{RS}

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RD surgery in a COVID-19-positive patient

(Continued from page 13)

- Creating a safer environment in the exam room and OR for both provider and patient has its challenges but is possible and achievable.
- We must allocate an immense amount of resources to care for COVID-19 patients, especially those undergoing surgery. We were fortunate to have excellent resources and infrastructure in place to face this challenge.
- COVID-19-positive patients deserve the same care and compassion that we provide to any other patient. It can be isolating to be placed in a negative-pressure room and to see your physician donned in protective gear. We must remember to maintain the human connection. Even as we maintain appropriate social distancing, we should ensure that the patient feels cared for and not ostracized.

At the one month post-op, the patient and his wife were overjoyed that they could be examined in a normal room and we could interact with them with less personal protective equipment than we had donned for prior visits.

Bottom line

If we learned one thing from COVID-19, it's that human life is precious and that it is possible to connect with others despite barriers. While we're retina specialists, we're physicians first and play an impactful role in not only treating patients' eye disease, but also their spiritual and mental well-being. Our duty to treat patients with retinal disease remains even during a pandemic, and we're able to employ safe measures regardless of their COVID-19 status.

Since the start of the COVID-19 pandemic, here at UW, our Eye Institute and hospital have implemented many changes. We will continue to apply the lessons learned from our early encounters with COVID-19 patients to the management of future patients affected by this novel virus.

We hope to learn more about this disease. We recently received approval from the UW internal review board and COVID-19 Research Review Working Group to study the ocular manifestations of this virus in our patient population. ^{RS}

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A Discussion Among Experts on the Treatment of Uveitis Affecting the Posterior Segment

0.18 mg
YUTIQ™
(fluocinolone acetonide
intraocular implant) 0.18 mg

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Introduction

Uveitis is an umbrella term for any type of inflammation involving the uvea, and it is a leading cause of blindness worldwide.¹ In the United States, uveitis accounts for approximately 10% of preventable vision loss and has an estimated prevalence of 133 per 100,000 individuals.^{1,2} The majority of cases (91%) are from a noninfectious etiology, of which 19% can be classified as nonanterior, encompassing intermediate, posterior, and panuveitis.²

Because uveitis encompasses so many different etiologies and presentations, there is no one standard uveitis patient. When all types of uveitis are considered, women are more likely to be affected than men; however, a patient with chronic noninfectious uveitis affecting the posterior segment is more likely to be a middle-aged (47.8 years old) man.^{2,3} Patients with chronic noninfectious uveitis are more likely to have ocular comorbidities such as retinal disorders, glaucoma, and visual disturbances, as well as systemic autoimmune diseases, including, most commonly, rheumatoid arthritis and sarcoidosis. They are also likely to require more than 13 prescriptions and have more than 30 visits to a healthcare provider per year.³

Regardless of the anatomic location, steroids are considered the mainstay of noninfectious uveitis therapy, and the overall goal is to achieve long-term remission of inflammation using steroids as little as possible. Anterior uveitis is usually treated with topical steroids, whereas noninfectious uveitis affecting the posterior segment can be treated with oral or local (sub-Tenon or intraocular injections) steroids. If inflammation remains uncontrolled by steroids, they can be followed by immunosuppressives and/or biologics.¹ Another option for long-term control without resorting to systemic treatment is YUTIQ® (fluocinolone acetonide intraocular implant) 0.18 mg, an intraocular steroid implant.

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intraocular implant) 0.18 mg is indicated for the treatment of chronic non-infectious 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.

Please see Important Safety Information for YUTIQ continued on pages 2, 4, and 6.

Please see Brief Summary for YUTIQ on page 8.

What Is YUTIQ[®] (fluocinolone acetonide intravitreal implant) 0.18 mg?

YUTIQ is a US Food and Drug Administration–approved option for the treatment of chronic, noninfectious uveitis, affecting the posterior segment of the eye. It is a nonbioerodible implant that is injected into the vitreous and is designed to deliver a sustained release of fluocinolone acetonide for up to 36 months. Clinical trial data from 2 phase 3 sham-injection–controlled, double-masked studies showed that YUTIQ reduces the recurrence of uveitis at 6 and 12 months after injection (**Figure 1**) and extends the time to the first recurrence of uveitis within the first 12 months after injection (**Figure 2**).⁴

Figure 1. YUTIQ reduces uveitis recurrence at 6 and 12 months.

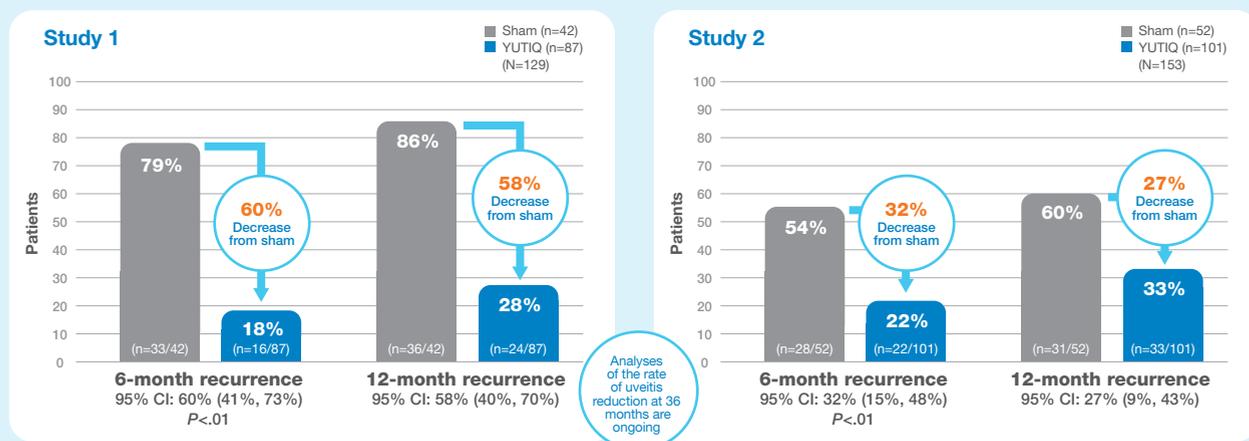
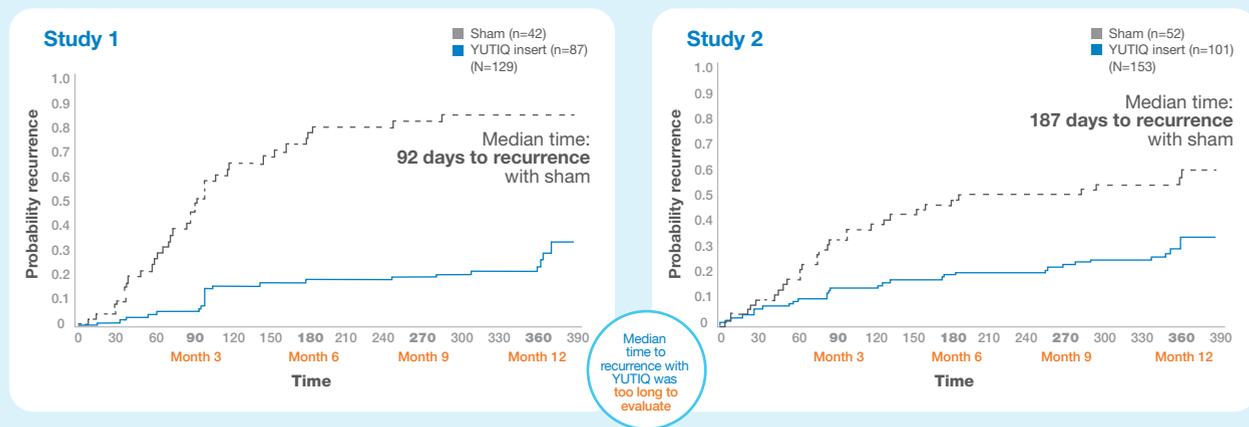


Figure 2. YUTIQ extends the time to first recurrence within 12 months.



IMPORTANT SAFETY INFORMATION (CONT'D)

Contraindications (cont'd)

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.

Please see Important Safety Information for YUTIQ continued on front cover; pages 1, 4, and 6.

Please see Brief Summary for YUTIQ on page 8.

The Experts Discuss How to Use YUTIQ[®] (fluocinolone acetonide intravitreal implant) 0.18 mg in Existing Treatment Paradigms*

DR. SINGER: For patients with anterior chamber cell and/or flare indicating mild but persistent anterior inflammation, I usually start with topical steroids. If the patient is unresponsive, I switch to periocular steroid injections, especially if there is mild vitritis, but I try to avoid too many sequential periocular injections because I believe they increase IOP.

DR. DHOOT: Yes, I've also moved away from doing too many periocular steroid injections because of the POINT study, so I've shifted to intraocular steroid injections for forms of uveitis affecting the posterior segment.⁵

DR. SHARMA: When there's anterior uveitis, I start with topical steroids, but if the inflammation is refractory or not responding well, I will treat with oral steroids to ensure they respond well. If they flare when tapering, I will then consider either periocular or more likely intraocular steroids. However, I will also start systemic therapy to avoid repeated local injections.

DR. ALBINI: I tend to see local steroids that are injected either periocularly or intraocularly in 1 of 2 roles: either as a primary means to control ocular inflammation or as an adjunct to systemic medications, if the patient still has breakthrough ocular inflammation. Most systemics aren't great at controlling inflammation in the retina, so you often need to add a local steroid in those cases. For milder cases of intermediate uveitis, intraocular injection is great as a primary treatment, but it can also be used as adjunct medication for posterior or panuveitis. I still use intravitreal steroid implants for more serious cases because it's stronger, but they do have a more severe side effect profile and require surgical implantation, which makes them more complicated than injections.

DR. HARIPRASAD: The bolus effect from intraocular steroid injections helps to get the inflammation under control and as retina and uveitis specialists, we're all comfortable with its application and side effect profile. But, because it has a short duration of action, I find that for patients with long-term chronic uveitis, there is an inconsistent effect and they tend to have flares when the drug starts to run out.

DR. SINGER: Now that YUTIQ is available, I definitely use dexamethasone intravitreal implants before I use it. The currently available dexamethasone intravitreal implants are short acting, so you can get a better idea of how the patient's IOP will respond and if they'll have any steroid-related side effects. I like to use at least 2 intraocular injections to get the patient dry and then use YUTIQ to keep them dry. I also like to bridge them with the intraocular injection, so I'll wait 6 to 9 weeks after it before doing the YUTIQ injection. That way, the patient's inflammation is under control and the low-level sustained steroid release from the YUTIQ implant helps maintain quiescence. In my experience, if the eye isn't already quiet, YUTIQ will still work, but there is no immediate quieting; it is more of a slow and steady improvement.

DR. ALBINI: Yes, YUTIQ really shines in maintenance and helping to prevent recurrence, but the initial impact is not as great as that of the intraocular steroid injections, so, it's better to get inflammation under control in other ways. YUTIQ is not ideal for more difficult, acute cases; instead, it's better for maintenance and may reduce the need for adjunct medications.

DR. SHARMA: That's my thought, too. In my practice, I tell my patients that YUTIQ is for maintenance since it's a low dose and it may reduce the number of other treatments the patient needs. The easiest patients to use YUTIQ on are probably those who have had multiple intraocular steroid injections. That way, like Dr. Singer has said, you can get a better idea of how they'll react to YUTIQ, but over a shorter period of time.

*The opinions herein are those of the authors and are not the opinion of EyePoint or its representatives.

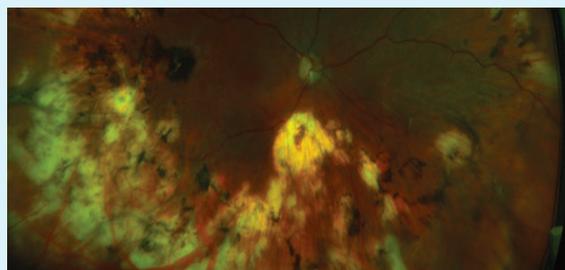
IOP=intraocular pressure.

Case Studies

Dr. Singer

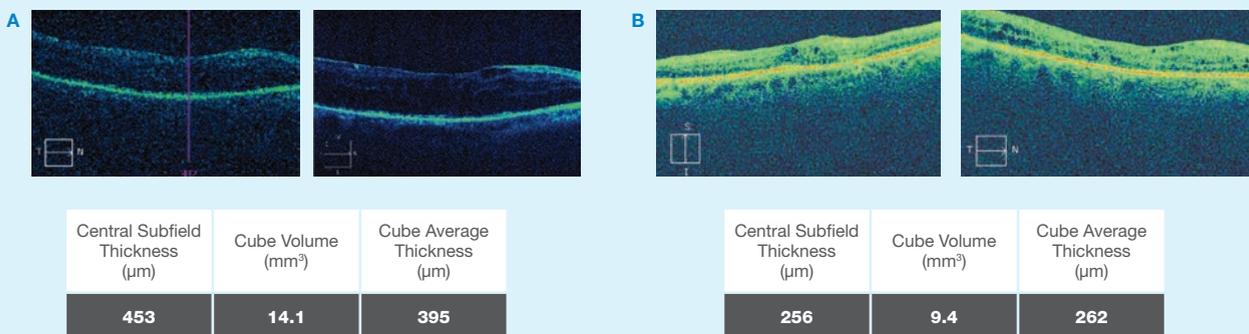
A 67-year-old white male presented with a history of bilateral retinal detachment repair and chronic, bilateral, posterior uveitis. BCVA was 20/150 OD and 20/60 OS and IOP was 12 mm Hg OD and 14 mm Hg OS. He had 1+ vitreous cell OD and significant intravitreal cysts visible in color fundus (Figure 3). The patient was treated with repeated dexamethasone injections. The patient's vision had deteriorated to 20/200 OD and 20/80 OS and he had OU 2+ vitreous cells and snowballs. His IOP was 12 mm Hg OD and 13 mm Hg OS.

Figure 3. Color fundus at initial presentation, November 2016.



The patient was given a YUTIQ injection OD. Three months after treatment, BCVA in OD had improved to 20/60, vitreous cells decreased to trace, and IOP was 13 mm Hg. The patient's OCT also improved to 256 μm (Figure 4A and 4B). Based on these results, the patient's fellow eye was also treated with YUTIQ at this time. The patient is now undergoing regular follow-up on both eyes.

Figure 4. OCT imaging of OS. A) Immediately prior to YUTIQ injection. B) Three months after YUTIQ treatment.



BCVA=best-corrected visual acuity; CME=cystoid macular edema; OCT=optical coherence tomography.

IMPORTANT SAFETY INFORMATION (CONT'D)

Warnings and Precautions (cont'd)

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.

Please see Important Safety Information for YUTIQ continued on front cover; pages 1, 2, and 6.

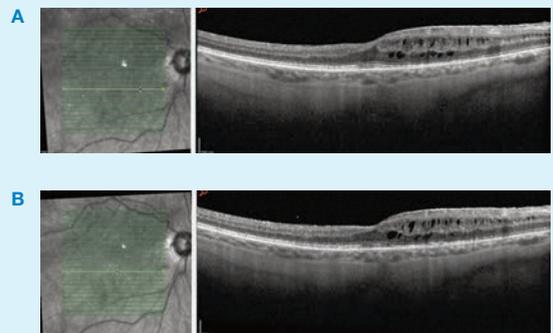
Please see Brief Summary for YUTIQ on page 8.

Case Studies

Dr. Dhoot

A 63-year-old white female presented with mild uveitis due to a history of scleral buckling and vitrectomy for retinal detachment/proliferative vitreoretinopathy OD. Her vision was CF OD and she had trace vitreous cells OD. She was treated with intravitreal steroid injections with limited success for several years. The patient was switched to YUTIQ, and she was followed up at 1 month. The patient's BCVA remained the same, but her OCT showed minimal improvement (**Figure 5**). While the initial follow-up visit showed some improvement, further follow-ups will be necessary to see the long-term effects of YUTIQ.

Figure 5. OCT imaging of OD. A) Immediately prior to YUTIQ injection. B) 1 month after YUTIQ treatment.

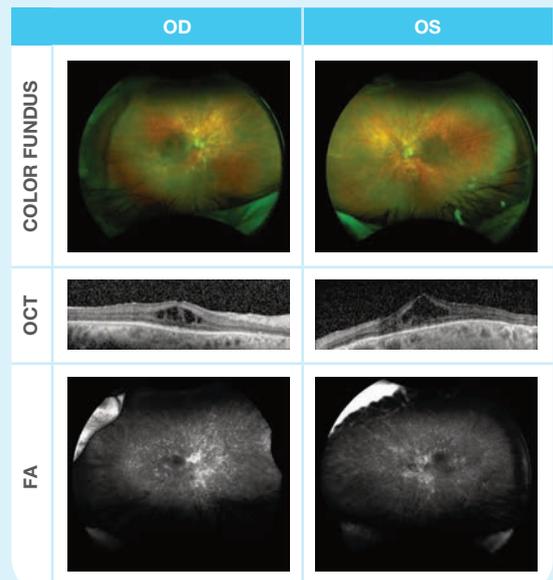


Dr. Albini

A 60-year-old white male presented with birdshot chorioretinopathy. His vision was 20/40 OU, but due to his occupation, he had difficulty following any treatment plan. Before the YUTIQ injection, the fundus photographs showed that the presence of CME that was worse OS than OD and the FA showed mostly window defects where he was starting to develop atrophy in the birdshot lesions and light vascularization. The OCT was also consistent with these findings (**Figure 6**).

A YUTIQ injection was initially performed only in OS because it had worse macular edema. At the 4-month follow up, OS showed modest improvement with CST decreasing from 410 μm to 351 μm and an improvement in BCVA from 20/40 to 20/30; however, these modest gains are significant for a patient who has previously been noncompliant with other treatment regimens. Since at this time OS had showed improvement, it was decided to inject YUTIQ into the fellow eye, and follow up for both eyes is on going.

Figure 6. Imaging before YUTIQ treatment.



CST=central subfield thickness; FA=fluorescein angiography.

Case Studies

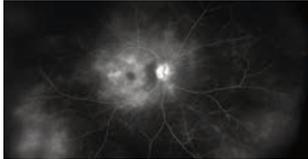
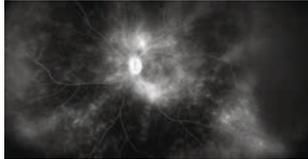
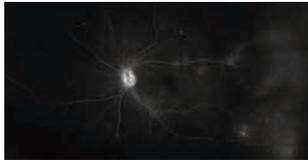
Dr. Sharma

A 59-year-old African American female presented with sarcoidosis with panuveitis and significant (2+) vitreous cell OU. At that time, the patient's BCVA was 20/80 OD and 20/40 OS. She was prescribed oral steroids followed by immunosuppressives and eventually adalimumab. This treatment course improved her vision to 20/60 OD and 20/30 OS and decreased vitreous cell to trace OU. But the patient was incompletely controlled with immunosuppressives and adalimumab, so she required repeated intraocular steroid injections OU to control her uveitis.

She received YUTIQ implants OU to provide long-term control over her uveitis. Immediately prior to the YUTIQ implants, the patient's BCVA was 20/125 OD and 20/25 OS and she had 0.5+ vitreous cell OD and 1+ vitreous cell OS.

FA imaging showed that vascular leakage in both eyes improved at 6-week, 6-month, and 9-month follow-up visits (**Figure 7**). After treatment, her BCVA in both eyes was 20/25.

Figure 7. FA before YUTIQ and at each follow-up visit.

FOLOW-UP VISIT	OD	OS
BEFORE YUTIQ		
6 WEEKS		
6 MONTHS		
9 MONTHS		

IMPORTANT SAFETY INFORMATION (CONT'D)

Adverse Reactions

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

Please see Important Safety Information for YUTIQ continued on front cover; pages 1, 2, and 4.

Please see Brief Summary for YUTIQ on page 8.

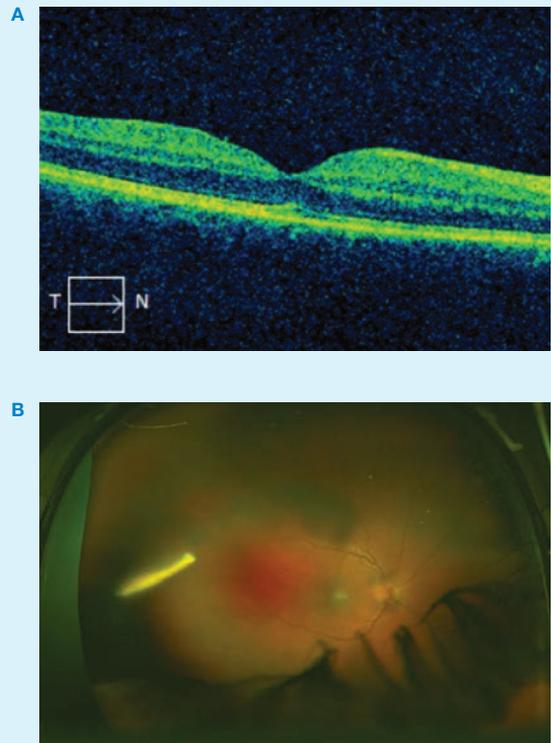
Case Studies

Dr. Hariprasad

A 34-year-old female presented with a 6-week history of blurred vision, light sensitivity, and redness in her right eye. She had been previously diagnosed with panuveitis and was started on prednisolone acetate drops every hour while awake. Her visual acuity was 20/40, her pupil was 3 mm and fixed, and the IOP was 11 mm Hg in OD. Slit lamp examination found +1 injection on her conjunctiva/sclera, 1-2+ anterior chamber cell, and 360° posterior synechiae with iris bombe. There also was pigment and fibrotic material on the anterior capsule and fibrotic material on the posterior capsule. Dilated fundus exam showed 2-3+ vitreous cell with haze, an elevated hyperemic disc, retinal nerve fiber layer hemorrhage, and a blunted foveal light reflex (Figure 8A). There were no abnormal findings OS.

The patient was continued on prednisolone acetate drops every hour while awake. Follow-up found her visual acuity was 20/30 and she had improved anterior chamber inflammation, but there was persistent 2-3+ vitreous cell with optic nerve edema and macular thickening. She was then prescribed YUTIQ to treat her persistent posterior uveitis. Follow-up after the YUTIQ injection showed some improvements in vitreous cell and haze (Figure 8B).

Figure 8. A) OCT of OD before YUTIQ injection. B) Color fundus of OD after YUTIQ injection.



Injection Tips*

- **Dilate the eye**—once it is injected, the YUTIQ implant is easier to visualize when the eye is dilated
- **Use subconjunctival anesthesia**—YUTIQ is injected once every 3 years, so it is worth the time to apply some subconjunctival anesthesia to make the injection process a bit easier on the patient
- **Go straight in**—the injector does not have a bevel, so twisting while inserting it is not necessary
- **Control the injector**—choke up on the injector to have more control over it
- **Use a cotton swab or forceps**—while injecting, use a cotton swab or forceps in the other hand to push the conjunctiva out of the way while also pushing in to increase the tension at the injection site

*These tips are from various clinicians who have used YUTIQ and are not necessarily the view of the authors.

REFERENCES 1. Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. *Surv Ophthalmol.* 2016;61(1):1-17. 2. Thorne JE, Suhler E, Skup M, et al. Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol.* 2016;134(11):1237-1245. 3. Thorne JE, Skup M, Tundia N, et al. Direct and indirect resource use, healthcare costs and work force absence in patients with non-infectious intermediate, posterior or panuveitis. *Acta Ophthalmol.* 2016;94(5):e331-e339. 4. YUTIQ [package insert]. EyePoint Pharmaceuticals. 2018. 5. Thorne JE, Sugar EA, Holbrook JT, et al; Multicenter Uveitis Steroid Treatment Trial Research Group. Periocular triamcinolone vs. intravitreal triamcinolone vs. intravitreal dexamethasone implant for the treatment of uveitic macular edema: The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial. *Ophthalmology.* 2019;126(2):283-295.

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

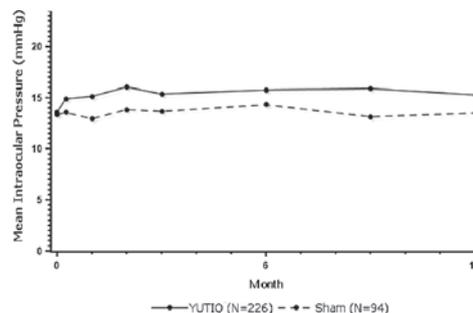
Ocular		
ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham Injection (N=94 Eyes) n (%)
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		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

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Patented.

Managing nAMD in the COVID-19 era

Has the time come for AMD home monitoring?

An update on the progress of home-based OCT and how it could reduce treatment burden during and beyond the pandemic.

By Judy E. Kim, MD



Judy E. Kim, MD

Take-home points

- » Reducing the treatment burden for chronic diseases such as neovascular age-related macular degeneration must be balanced against maintaining visual acuity.
- » Close monitoring for progression or relapse is critical in maintaining VA and vision gains.
- » A home-based optical coherence tomography system is a patient self-operated device designed to support and enhance standard of care.
- » Remote diagnostic clinics that provide monitoring services, including patient compliance of the device at home, are important elements in helping retina specialists comanage patients in this new era of pandemic.

As retina specialists, we readily agree that the introduction of anti-VEGF agents for a variety of retinal diseases has helped us preserve sight for countless patients. However, for treatment of chronic conditions, such as neovascular age-related macular degeneration that affects our elderly population, we also know more work is needed to reduce the treatment burden while maintaining visual acuity.

In nAMD, approximately 41 percent of newly diagnosed and treated patients will gain at least 3 lines of vision, but others may never achieve 20/40 or better VA even with consistent treatment.¹⁻³ Mounting evidence may help our understanding of this conundrum. Studies show that baseline VA at the time of diagnosis is strongly associated with vision outcomes with intravitreal anti-VEGF agents.^{4,6} Therefore, diagnosing and treating patients earlier in the disease process could be a key to improving visual outcomes in nAMD.

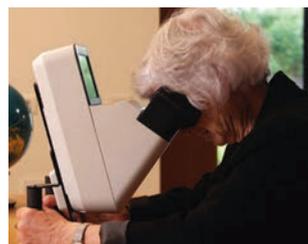


Figure 1. A patient self-images using the investigational Home OCT device.

We know from numerous clinical trials and published reports on nAMD that frequent and consistent intravitreal injections with anti-VEGF agents and close monitoring for progression or relapse are critical in maintaining VA and vision gains. Ultimately, these require continued in-office visits.

While office visits were already challenging for some elderly patients under the best circumstances—transportation, for example, can be difficult for them to arrange—they've become substantially more so in the wake of the COVID-19 pandemic as the elderly population is at an increased risk for complications from the virus. As we slowly reopen our offices and practice

Bio

Dr. Kim is a professor of ophthalmology and visual sciences, specializing in vitreoretinal diseases and surgery, director of teleophthalmology and research, and a professor at the Graduate School of Biomedical Sciences, Medical College of Wisconsin, Milwaukee.

DISCLOSURE: Dr. Kim is a paid consultant and investigator for Notal Vision.

under the “new normal” methods prioritizing the safety of our patients and staff, retina specialists need to consider alternative ways of providing high-quality care. One such way is through remote monitoring and telehealth.

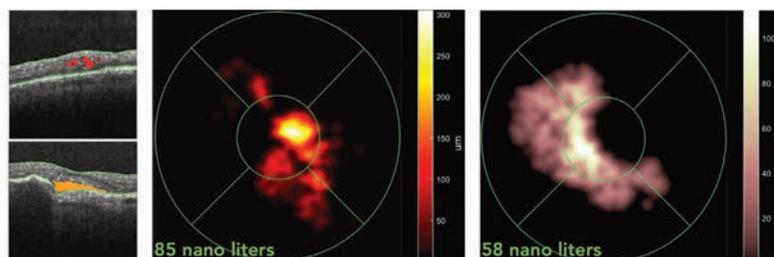
Home-based OCT

Optical coherence tomography improves the diagnosis and management of many retinal conditions. This is especially true with nAMD, for which diagnosis and treatment decisions, including treatment interval, depend heavily on OCT findings in the clinic.

What if we could perform OCT in the patient’s home? A new OCT system that patients can use at home rather than in the office is in development (*Figure 1*, page 25, Home OCT, Notal Vision). This patient-operated OCT system is designed to support and enhance standard of care. Patients with nAMD use the device at home to capture macular images, which are then relayed to the treating physician and the remote diagnostic center to identify fluid recurrence or progression and to provide inter-visit disease information.

The diagnostic clinic provides the device to the patient following a physician referral. The remote clinic educates the patient about device use, monitors patient self-imaging compliance and can send reminders if the patient isn’t self-monitoring. Thus, home-based OCT may be a solution for reducing the burden of coming to the office for patients while they’re being safely monitored remotely. It may also increase the chances of timely detection of recurrent fluid and prompt a visit for intravitreal injection, thus reducing the risk of VA loss.

Figure 2. An artificial-intelligence-based algorithm analyzes optical coherence tomography images for presence, localization and quantity of intra- and subretinal fluid.



Our experience evaluating the device

My colleagues and I recently evaluated the investigational Home OCT in patients with either nAMD or non-nAMD to assess its ease of use and the overall experience of operating the system for self-imaging by the patients. We also compared the device to in-office OCT imaging for disease activity.

We conducted a company-sponsored prospective study of 531 consecutive eyes (290 patients) with nAMD and non-nAMD with VA better than or equal to 20/400. The average patient age was 79 years with a mean VA of 20/40; 17 percent had VA of 20/80 or worse. Photographers imaged patients without dilation using a commercial OCT (388 eyes were imaged with the Cirrus [Zeiss] and 81 eyes with the Spectralis [Heidelberg Engineering]). The patients then viewed a two-minute video tutorial of the Home OCT, followed by self-operating the device to capture images of their own eyes. Those images were then compared to the commercial OCT images by a masked reader to determine the presence of fluid.

The results were encouraging, with 91 percent of patients able to complete the Home OCT imaging in at least one eye. We found that VA had a role in successful imaging: 81 to 93 percent of patients with VA >20/320 were able to capture successful images compared to only 50 percent of those with <20/320. More than 90 percent of patients agreed or strongly agreed that the video tutorial was helpful and clear and that the scan was quick, comfortable and easy. A total of 46 percent of eyes had fluid. Thirteen eyes had a discrepancy in image reading between the Home OCT and commercial OCT; positive and negative agreement were 98 and 96 percent, respectively.

I should note, however, that although the Home OCT was designed for home use, the study was done in an in-office setting, so we don’t yet have real-world experience with the device. Based on our in-office experience, though, and coupled with the use of a remote diagnostics clinic

that will follow-up with patients, I don't expect home use to be much different from what we saw in our study.

As the next step in this research, the first longitudinal at-home study started in June. It demonstrates for the first time, the feasibility of patient daily OCT self-imaging, cellular transmission of data to the cloud for image analysis and remote physician review. We eagerly await the study results.

AI supports treating physicians

To cope with the large amount of daily Home OCT images that require analysis, an artificial-intelligence-based algorithm that identifies, localizes, quantifies and maps fluid on each scan has been developed (*Figure 2*). It can track intra- and subretinal fluid over time and enables the physician to set thresholds for sending automated alerts. We can look at fluid in isolation regardless of retinal alterations like fibrosis that can mask disease activity on retinal thickness maps.

Real-world impact on patients

Despite the study limitations, my colleagues and I believe the Home OCT can provide valuable information to patients and physicians on disease progression, helping to support retina specialists to better personalize AMD management, maintain VA throughout the treatment course and reserve in-clinic visits for injections rather than routine monitoring.

I also believe that this and similar devices may improve our follow-up rates. Some patients with AMD may end up with fewer visits, resulting in fewer transportation challenges and hopefully less treatment burnout. Others will be more motivated to come in knowing that they have fluid that needs to be treated.^{7,8} Being able to better identify patients needing more frequent injections compared to those needing fewer injections will benefit us all.

(Continued on page 42)

Home monitoring: Promise and potential hurdles

Retina specialists David Eichenbaum, MD, and Daniel Kiernan, MD, agree that home-based monitoring with optical coherence tomography has great potential, but they also hope the developer of the Home OCT system, Notal Vision, applies important lessons from the launch and rollout of the ForeSee Home microperimetry system to the ongoing development of the Home OCT system.

Drs. Eichenbaum and Kiernan are co-authors of a yet-unpublished review of patients who used ForeSee Home. While they say home-based OCT still has hurdles to overcome, they also acknowledge that during the COVID-19 stay-at-home orders, home monitoring with the ForeSee Home (FSH) has proved valuable in continuing care for some patients, obviating the need for routine office visits.



Dr. Eichenbaum



Dr. Kiernan

“For those patients who continued using it, we were still able to receive alerts and to reach out to them directly and have them come in for visits,” says Dr. Kiernan, who practices on Long Island, New York. “The percentage of patients who came in because of the ForeSee Home alert increased dramatically in terms of the overall number of patient visits.”

Dr. Kiernan adds Dr. Eichenbaum, who practices in St. Petersburg and Clearwater, Florida, “The potential for home monitoring is great, especially as we get longer-duration therapy; patients may require fewer overall visits to the doctor's office, especially if we have validated home monitoring with imaging to see how the therapy is working.”

But before home-based OCT is widely embraced, they say it must be validated and prove it can achieve a baseline. Additionally, patients must be able to use it, the results must be reliable and reproducible, and it must overcome potential cost barriers.

“It must be sensitive and specific to the detection of and changes in the volume of intraretinal and subretinal fluid,” Dr. Eichenbaum says. He also mentions the “cost barrier,” adding, “It must be something patients can afford.”

Dr. Kiernan dives into cost issues a little deeper. “They need to work out whether the device sends an alert to the physician or if the images and test results are sent to the physician without an alert, and that there is a reimbursement or professional fee for the physician's time to look at and interpret those images,” he says. “That was a problem with the original ForeSee Home.”

They say patient compliance is another foreseeable problem the device must overcome. “There's going to be a technical component despite all the customer support and technical assistance that some patients won't be able to overcome, but we should all give our patients as many options as possible,” says Dr. Kiernan.

They also offer suggestions for what continuing trials of the device should concentrate on. “They should investigate what the clinical outcomes look like for the population that uses Home OCT with an established diagnosis of wet age-related macular degeneration,” Dr. Eichenbaum says. “Does an established wet AMD population that has more home monitoring tests and fewer in-office visits do just as well as a traditionally monitored population, or better? Or do they perform worse because of limitations with home-monitoring technology or its use?”

But the potential for home-monitoring remains. “Especially in these times of the pandemic and as different resurgences occur, telemedicine has become front and center with many subspecialties, including ophthalmology,” says Dr. Kiernan. “The Home OCT will allow us to carry out a lot more telemedicine appointments, be able to bill for our time and, most importantly, be able to more effectively communicate with our patients with real-time diagnostic retinal testing performed by the patient from the comfort of their home.”

— Richard Mark Kirkner

Long-term anti-VEGF effect: Six questions answered

A review of the evidence that suggests the beneficial effects of consistent treatment extend out to 10 years.

By Ivan J. Suñer, MD, MBA, and Marc C. Peden, MD



Ivan J. Suñer,
MD, MBA



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MD

Take-home points

- » Long-term continuous treatment with anti-VEGF agents is safe and effective.
- » The risk of vision loss is higher from undertreatment than from continuous treatment such as fixed-interval dosing or treat-and-extend dosing.
- » The risk of vision loss from geographic atrophy is not higher than in treated vs. untreated fellow eyes.
- » Long-term anti-VEGF delivery with platforms like sustained-release implants and gene therapy may improve long-term outcomes by eliminating noncompliance, providing continuous therapy and reducing treatment burdens.

With anti-VEGF therapy patients with neovascular age-related macular degeneration typically have significant improvements in visual acuity and quality of life. While the short-term results are nothing short of spectacular, several important questions regarding long-term management of these patients persist. They include:

- Which is the best agent?
- How often should one treat?
- Does long-term dosing of these agents cause vision loss and damage?
- Are new platforms on the horizon for long-term delivery of these agents?

This article answers those questions based on findings of pivotal clinical trials.

Are all anti-VEGF agents equal? How often should we treat?

In 2006, the landmark ANCHOR and MARINA studies demonstrated the efficacy and safety of monthly ranibizumab (Lucentis, Roche/Genentech) with monthly dosing. Patients gained 10.7 and 6.6 let-

ters, respectively, at two years.¹⁻² Subsequently, the parallel VIEW1 and VIEW2 studies showed mean improvement in vision at two years with aflibercept (Eylea, Regeneron Pharmaceuticals) q8 weeks after three initial monthly loading doses.³

Subsequent trials allowed us to evaluate the efficacy of these drugs employing less frequent dosing intervals including quarterly, *pro re nata* (PRN) and treat-and-extend regimens. The PIER study examined quarterly dosing with ranibizumab after three monthly loading doses, and, while superior to observation, PIER patients lost 2.3 letters from baseline at one year.⁴

One of the earliest exceptions was PrONTO, a Phase I/II trial that evaluated 40 patients over two years with monthly monitoring and PRN retreatment based on visual acuity, clinical examination and optical coherence tomography parameters.⁵ The visual acuity results approached those of ANCHOR and MARINA with nearly half the number of injections, but the study lacked a monthly treatment con-

Bios

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Dr. Peden is a consultant/speaker for Alimera, Allergan and Genentech.

trol arm. These results have not been duplicated in subsequent PRN trials.

The HARBOR trial compared monthly and PRN dosing of ranibizumab. The monthly 0.5-mg group gained 9.1 letters at 24 months vs. 7.9 letters for the PRN group. While this difference was not statistically significant, the median number of injections (but not the number of visits) was reduced from 21.4 to 13.3.⁶

CATT and IVAN were similar studies that compared monthly and PRN dosing of ranibizumab and off-label bevacizumab (Avastin, Roche/Genentech). At two years, PRN dosing was found to be noninferior to monthly treatment in both studies (except for PRN bevacizumab in CATT), although there was a trend toward better vision in the monthly groups.^{7,8}

TREX compared monthly ranibizumab to a treat-and-extend (T&E) regimen.⁹ Once again, the visual acuity difference wasn't statistically significant (10.5 in the monthly group and 8.7 in the T&E group), but trended toward better vision in the monthly group. The mean number of injections was 25.5 vs. 18.6 over two years. Also, no monthly cohort patients lost more than 2 letters, while five T&E patients lost at least 3 lines of vision.

While these studies have shown statistically similar results with monthly dosing in the short term, absolute data outcomes have been almost unanimously superior with monthly dosing of anti-VEGF agents.

What happens after two years?

The data beyond two years from these clinical trials aren't as easy to interpret and apply as the clinical trial data, primarily because these extension studies mainly

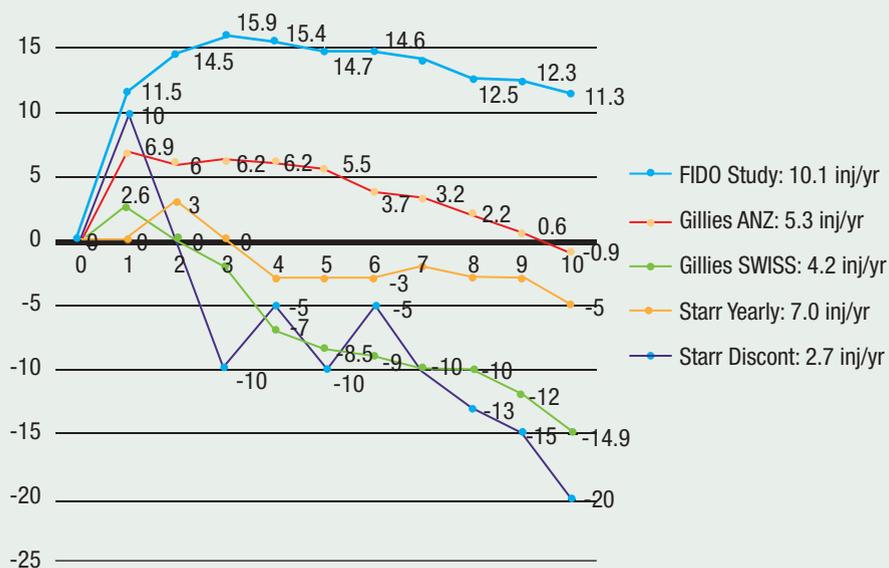


Chart shows the variation in 10-year visual acuity outcomes from observational studies of anti-VEGF treatment for neovascular age-related macular degeneration.

evaluated long-term drug safety. So, the follow-up and treatment schedules were not as rigorous.

HORIZON was the extension study for patients in the MARINA, ANCHOR and FOCUS trials. These patients didn't follow a protocol; they received treatment at the investigators' discretion during evaluation visits every three to six months. At four years, HORIZON patients essentially lost the initial VA gains and regressed to baseline vision (-0.1 letters).¹⁰ Further data analysis found an association between better vision and more injections.

The CATT five-year study assessed patients monitored and treated at the investigators' discretion after the first two years of the trial. On average, patients lost 3 letters compared to baseline vision. Patients were seen an average of eight times per year and received an average of five treatments per year.¹¹ Some discussion ensued as to whether the vision loss was due to undertreatment or development of macular atrophy, but the trial wasn't powered to tease out this difference.¹²

The central message from these long-term observational studies is that clearly, on average, more injections translated into better vision.

The VIEW 1 extension study monitored patients more rigorously. Participants received fixed-interval >q8-week dosing, but they could receive more frequent treatments if they met prespecified criteria. In this extension, patients retained much better vision, with mean vision of gain 7.1 letters from baseline (compared with a 10.4-letter gain at the one-year primary endpoint).¹³

What happens in the long-term and does dosing frequency matter?

The best long-term data we have is from observational studies. The SEVEN-UP Study was an extension of the ranibizumab trials. Although there was no prespecified visit schedule or injection protocol, the data provide some information. At seven years, patients on average lost 8.6 letters from baseline. Patients receiving no injections over the subsequent three years lost 8.7 letters from baseline; those receiving one to five injections lost 10.8 letters; those having six to 10 injections lost 6.9 letters; and those receiving more than 11 injections gained 3.9 letters from baseline.¹⁴

The Fight Retinal Blindness Study Group from Australia observed patients treated with anti-VEGF for seven years. These patients lost an average of 2.6 letters from baseline, having received an average of five injections a year after year two, when they had gained 4 letters from baseline.¹⁵

Finally, the FIDO study was a single-center observational study using q4-week fixed-dosing for the first two years and >q8 weeks beyond that. These patients gained 12.1 letters from baseline (from a peak of 16.1 letters at two years) with an average of 10.5 injections per year.¹⁶

The central message from these long-term observational studies is that clearly, on average, more injections translated into better vision.

We now have 10-year data

Recently, three large observational stud-

ies have reported 10-year data and the results remain consistent: More injections translate to better visual acuity. Mark Gillies, MD, and colleagues reported observational data from Australia-New Zealand and Switzerland. In the ANZ patients, mean vision decreased by 0.9 letters from baseline at 10 years with a median of 5.3 injections/year on a T&E regimen compared to the Swiss patients, whose vision decreased by a mean of 14.9 letters with a median of 4.2 injections per year on PRN. Their conclusion was that continuous treatment and more injections achieved better vision.¹⁷

Matthew Starr, MD, and colleagues evaluated a cohort that included patients who had at least two injections. On average, the patients received five to seven injections a year. Eyes receiving at least one injection a year lost approximately 7 letters from baseline, whereas eyes that didn't receive at least a yearly injection lost 15 letters from baseline.¹⁸

Our 10-year FIDO cohort achieved a mean increase in vision of 11.3 letters from a peak of 15.9 with an average of 10.1 injections per year over the study period.¹⁹

It's important to note that there are inherent risks with cross-trial comparisons given different initial visual acuity and patient populations, but the slopes and trends hold to the correlation of more injections with better vision. The figure (*page 29*) summarizes 10-year data from the three trials.

Does frequent treatment result in progression to geographic atrophy?

The worry of geographic atrophy progression with anti-VEGF treatment has been a concern and a frequently invoked rationale for not treating frequently. Some evidence suggests that the risk of vision loss from undertreatment far outweighs this potential concern. The SEVEN-UP trial showed greater incidence of GA in fellow eyes than in eyes treated with anti-VEGF.¹⁴

Furthermore, the FIDO 10-year data



I was only seeing light flashes early on, but light

FLASHES

when you've not seen anything for
so many years—it was wonderful

—Keith H, retinal prosthesis recipient

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demonstrated a slightly lower incidence of GA with vision loss at 10 years in the treated eyes compared to untreated fellow eyes (15 vs. 19 percent).¹⁹ It's likely that the progression of true GA is independent of anti-VEGF treatment, and what is observed is drying-out of the neovascular complex that looks like GA but with a less-deleterious impact on vision.

Bottom Line

Continuous, regular treatment with anti-VEGF agents provides outstanding results in the management of wet AMD. The long-term data demonstrate that risk of vision loss is greater from undertreatment than from continuous treatment at regular intervals as currently applied in fixed-interval dosing or conservative treat-and-extend regimens. Long-term delivery platforms such as the port-delivery system and gene therapy appear promising in decreasing the barriers of noncompliance, burden of frequent visits and challenges of variable individual dosing requirements.

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(References continued on page 42)

What does the future of wet AMD treatment look like?

The collective body of data is compelling for providing aggressive early, frequent therapy followed by some form of continuous therapy either in a fixed interval or conservative treat-and-extend regimen. *Pro re nata* regimens resulted in inferior outcomes compared to monthly therapy, and true PRN requires monthly monitoring, which can be burdensome to patients and practices.

With the explosion of the baby boomer population resulting in increasing numbers of wet age-related macular degeneration patients, the ability to provide frequent therapy requires engineering the practice flow to accommodate frequent injections either with concomitant increase in staffing or with series of "injection-only" appointments in between evaluation visits.

Fortunately, there are novel therapies and treatment platforms on the horizon that may provide the sustained therapeutic levels of frequent dosing without the burden of frequent visits or treatments.

The surgically placed Port Delivery System with ranibizumab (PDS) implant (Roche/Genentech) is likely to be available in the near future. After encouraging Phase II results of the LADDER study, the Phase III ARCHWAY trial was launched and has now completed enrollment. In this trial, PDS is refilled in the office every six months with rescue therapy available for earlier recurrences. In LADDER, the median time to first implant refill based on prespecified parameters was 15 months.²⁰

Also promising, but perhaps further away in terms of commercialization, is the prospect of gene therapy to sustain production of anti-VEGF within the eye.

Different approaches include viral vectors and CRISPR technology to introduce the gene,²¹ intravitreal injection (Adverum Biotechnologies), as reported in the OPTIC trial,²² and subretinal delivery either via pars plana vitrectomy approach or *ab externo* suprachoroidal approach, such as in the RGX-314 trial (RegenxBio).²¹⁻²³

Trials are evaluating whether these treatments will achieve therapeutic levels of anti-VEGF production and whether the therapy will be persistent and durable. 

It's likely the progression of true GA is independent of anti-VEGF treatment, and what is observed is drying-out of the neovascular complex that looks like GA but with a less deleterious impact on vision.

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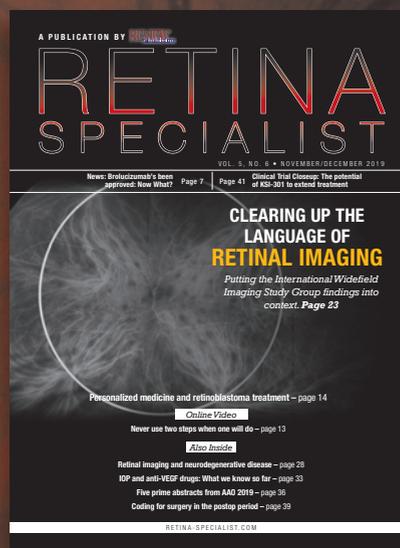
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Potential of OCT to identify genetic risk in AMD

A look at our work in optical coherence tomography-derived drusen burden in non-advanced age-related macular degeneration.

By Johanna M. Seddon, MD, ScM



Johanna M. Seddon, MD, ScM

Bio

Dr. Seddon is a professor of ophthalmology and visual sciences, director of retina and director of the Macular Degeneration Center of Excellence at the University of Massachusetts Medical School, Worcester.

DISCLOSURES: Dr. Seddon disclosed financial relationships with Gemini Therapeutics and Thea Pharmaceuticals, and funding support from the National Institutes of Health, Massachusetts Lions Eye Research Fund, International Retina Foundation and the American Macular Degeneration Foundation.

Take-home points

- » Spectral-domain optical coherence tomography can quantify variation in drusen morphology in an accurate and reproducible manner.
- » Our study showed that OCT-derived drusen area and volume measurements were related to stage of non-advanced age-related macular degeneration and were greater for eyes classified with intermediate vs. early AMD.
- » Among eyes with the same AMD grade (early or intermediate), genetic risk was associated with a higher drusen burden. *CFH* score and *ARMS2/HTRA1* were both independently associated with perifoveal drusen area and volume vs. no measurable drusen.
- » The advanced retinal pigment epithelium analysis algorithm or a similar method may be useful to categorize AMD stage with greater precision and ability to quantify measurements than clinical observation or photography.

The genetic component for progression of age-related macular degeneration to advanced disease, including geographic atrophy and neovascular disease, has been well documented.¹⁻⁴ Early and intermediate disease stages, primarily characterized by the formation of drusen, precede each advanced subtype. To lower the rate of disease progression and preserve vision, we need to identify therapeutic targets for earlier, high-risk disease stages.

With advances in *in vivo* imaging, spectral-domain optical coherence tomography can noninvasively visualize and discriminate the retinal and choroidal layers. OCT can also directly visualize and measure retinal pigment epithelium irregularities, including area and volume where drusen develop.

Our studies and others' have shown that OCT-derived drusen area and volume and retinal features, such as hyper-reflective foci and choroidal parameters, may aid in deter-

mining the likelihood of progression from early or intermediate to advanced AMD.⁵⁻¹⁰

Further characterization of drusen and retinal and choroidal morphology may help us identify biomarkers that may serve as early anatomic endpoints for clinical trials and facilitate the development of new AMD therapies. Our group studied whether higher drusen burden assessed by OCT in eyes with early and intermediate-stage AMD is associated with genetic risk. Here, I describe that work.

A sparse knowledge base

What we know about the association between OCT-derived retina parameters and AMD-related genetic variants is sparse.¹¹⁻¹² We previously reported that genes in the complement pathway are associated with a higher risk of progression from small and intermediate to large drusen, and large drusen to GA and neovascularization.¹³

We also found a novel association between the *ABCA1* gene in the high-density lipoprotein (HDL) pathway that reduced progression risk from normal to intermediate drusen and from intermediate to large drusen. The protective effects for transitions to advanced disease and larger drusen size have been found in other pathways.¹⁴⁻¹⁵

We evaluated the association between genetic risk and OCT-derived drusen area and volume in a clinical cohort of patients with early and intermediate AMD. Understanding these relationships, along with other OCT parameters, may lead to the clinical use of these measurements to identify earlier high-risk phenotypes and better define progression risk.

Characterizing drusen on OCT may help us identify disease biomarkers. We evaluated associations between genes implicated in advanced AMD risk and drusen area and volume measurements based on OCT in eyes with clinically diagnosed early and intermediate AMD.¹⁶

Study design and methods

• **Population and classification of AMD phenotypes.** All participants were previously enrolled in our ongoing genetic and epidemiologic studies of AMD beginning in 1985.¹⁷⁻²⁰ They were derived from clinic populations and nationwide referrals and were followed prospectively. The study protocol includes an ocular examination, fundus photography and OCT imaging, as well as interviews and blood sampling. AMD phenotypes were based on ocular examination and ocular imaging. Eyes were classified using the Clinical Age-Related Maculopathy Staging (CARMS) system.²¹ Risk factors were determined using our standardized questionnaire that included age, gender, education, body mass index (BMI) and smoking.¹

• **Evaluation of drusen area and volume measurements.** Beginning in 2007 our study protocols included OCT scans for the purpose of assessing parameters associated with various stages of AMD, progression

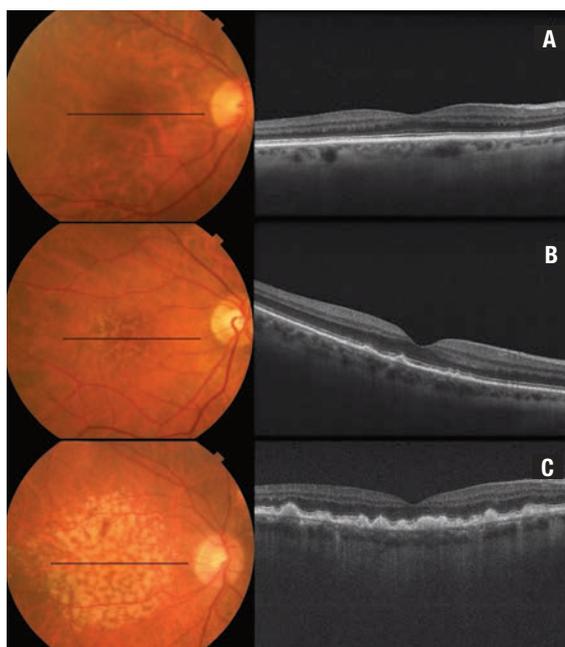


Figure 1. Color fundus photographs and optical coherence tomography scans corresponding to different measurements using the advanced retinal pigment epithelium analysis tool are shown as (A) no measurable drusen, (B) drusen area and volume less than median and (C) drusen area and volume at median or greater. (All figures used with permission of *Investigative Ophthalmology and Visual Science*)

and genetic factors. We conducted a retrospective review of Cirrus spectral-domain OCT 4000 and 5000 scans (Carl Zeiss Meditec) among individuals with one or both eyes with stage 2 or 3 disease. The OCT protocols included high-definition one-line and five-line scans, and macular cube (512 by 128:128 B-scans and 512 A-scans per B scan) over a 6-x-6-mm square, centered on the fovea.²²⁻²⁴ The OCT technician determined fovea position to match its known anatomic configuration.

Drusen area and volume measurements were determined by the Cirrus version 6.0 Advanced RPE Analysis algorithm, a fully automated algorithm based on a determination of the RPE floor and elevation measurements of RPE deformations. This yielded an automatic quantitative assessment of RPE deformations and calculated highly reproducible measurements of area and volume.^{23,24} The measurements provide an estimate of drusen burden for a 5-mm circle (perifoveal zone) centered at the fovea.

• **Genotyping and genetic data.** The study used array-based and gene-sequencing platforms as previously described to determine genotypes.¹⁷⁻²⁰ We chose com-

mon variants in genes previously associated with drusen and AMD in the complement and HDL pathways and the gene locus on chromosome 10q26 given their consistent association with advanced disease or biologically plausible relationship to drusen formation.^{13,17-20,25,26}

• **Statistical methods.** These analyses included 239 eyes of 179 patients. The study used two categorical comparisons in separate models for each outcome: eyes with some drusen but less than the median volume vs. no measurable drusen; and eyes with the median volume or more drusen vs. no measurable drusen. Eyes without advanced AMD at baseline were the reference adjusted for correlation between fellow eyes.²⁷ All models were adjusted for age, sex, smoking, BMI and education.

The study assessed two distinct outcomes of interest: drusen area and drusen volume in the perifoveal zone. Genetic variables were defined as having zero, one or two risk or protective alleles. We combined the two *CFH* variants that convey different information about AMD risk into a risk score.

Since we identified consistent significant associations in categorical analyses between drusen measurements and risk genotypes for *CFH* risk score and *ARMS2*, we looked in more detail at mean area and volume represented as continuous variables for these two genes and assessed the independent effects of each gene on drusen measurements.

Key findings

Figure 1 (page 35) displays representative color photographs and OCT scans corresponding to different measurements obtained using the Zeiss advanced RPE analysis tool.

• **Association between OCT drusen measurements and AMD grade.** Mean OCT-derived drusen area was significantly associated with AMD grade based on color photographs and was higher in intermediate vs. early AMD eyes after adjustments for age, sex, smoking, BMI and education ($p=0.008$) (Figure 2A). Similarly, mean drusen volume was greater in intermediate vs. early AMD ($p=0.005$) (Figure 2B).

• **Associations between drusen measurements and AMD genetic variants.** A higher *CFH* score (combining two *CFH* variants) was associated with greater drusen area in the perifoveal 5-mm zone controlling for age, sex, smoking, BMI and education (Table 1). Drusen area greater than median vs. no measurable drusen increased per category of *CFH* score. Risk for greater drusen area increased 1.6 times for each genetic score category, and risk for greater drusen burden with three or more risk alleles in *CFH* score was fivefold higher. Drusen volume yielded similar results.

The variant in the complement pathway gene *C3 R102G* was significantly associated with greater drusen only in the univariate analysis.¹⁸ A greater number of risk alleles for the variant in *ARMS2/HTRA1* was also associated with greater drusen area controlling for the previously noted variables. The variant at this locus carried a significant association with greater drusen area per each risk allele: a 2.45-fold increased risk ($p<0.001$). Similar results were seen for drusen volume.

• **Multivariate analyses of associations between drusen burden and genetic variants.** When analyzing each genetic variable while controlling for all of the other variants, only two remained independently associated with a significantly greater drusen area: *CFH* risk score and

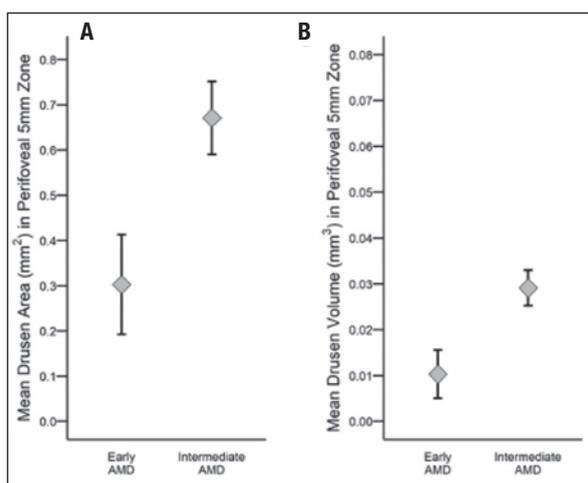


Figure 2. Associations between optical coherence tomography-derived drusen measurements and early and intermediate stages of age-related macular degeneration, for (A) drusen area ($p=0.008$) and (B) drusen volume ($p=0.005$). The diamond represents the adjusted mean controlling for age, sex, smoking, body mass index and education. The vertical line represents plus or minus one standard error of the adjusted mean.

the *ARMS2/HTRA1* variant (Table 2, page 38). Similar results were seen for drusen volume. The HDL genes *LIPC*, *ABCA1* and *CETP* were not significantly related when controlling for the other non-genetic and genetic variants.

• **Independent associations between drusen measurements, *CFH* score and *ARMS2*.** Both mean perifoveal drusen area and volume increased with *CFH* score. The trends for increasing drusen burden as the *CFH* score increased were significant after adjusting for the previously noted variables along with AMD grades ($p=0.004$ for area, 0.002 for volume). Carriers of two risk alleles had greater drusen area and volume than patients with one or none ($p=0.03$ and 0.04, respectively); carriers of three or four risk alleles had significantly higher drusen area and volume than those with one or none ($p<0.001$ for both).

Similar comparisons were assessed for the *ARMS2/HTRA1* variant. Mean drusen area and volume increased with the number of risk alleles after adjustment for other variables ($p<0.001$ for both drusen area and volume). Carrying two risk alleles vs. none was significantly related to greater drusen area and volume ($p=0.008$ and 0.004, respectively). Associations between OCT-derived perifoveal drusen measurements and genetic factors are depicted in Figure 3 (page 39).

When both genes were adjusted for each other (bivariate analyses), the associations between drusen measurements and *CFH* score were somewhat reduced. However, the trend for higher drusen area and volume with a higher score remained significant ($p=0.01$ and 0.005, respectively).

When the *ARMS2/HTRA1* genetic variant was adjusted for *CFH* score, results were similar to the univariate analysis. Trends for drusen area and volume increasing with the

Table 1. Multivariate analyses of associations between drusen area and genetic loci*

	No Drusen Measured (n=111)	Drusen Area < median (n=54)		Drusen Area ≥ median (n=74)	
		OR† (95% CI)	p-value	OR† (95% CI)	p-value
<i>CFH</i> Score	1.0 (ref)	0.93 (0.61 - 1.41)	0.73	1.58 (1.01 - 2.46)	0.04
<i>ARMS2/HTRA1</i>: rs10490924	1.0 (ref)	1.24 (0.72 - 2.15)	0.44	2.45 (1.35 - 4.45)	<0.001
<i>C3 R102G</i>: rs2230199	1.0 (ref)	1.00 (0.55 - 1.82)	0.99	1.57 (0.87 - 2.85)	0.14
<i>ABCA1</i>: rs1883025	1.0 (ref)	0.65 (0.31 - 1.38)	0.27	0.84 (0.41 - 1.73)	0.65
<i>LIPC</i>: rs10468017	1.0 (ref)	1.14 (0.61 - 2.12)	0.69	0.76 (0.43 - 1.36)	0.36
<i>CETP</i>: rs3764261	1.0 (ref)	1.17 (0.67 - 2.04)	0.57	1.28 (0.78 - 2.12)	0.33

Key: * Each genetic variant assessed in a model, controlling for age, sex, education, body mass index, smoking, and other genetic variants; † Odds ratio (OR) and confidence interval (CI) per risk or protective allele. *CFH* score categorized as 0,1,2,3-4 risk score categories. 1.0 is the reference category.

number of *ARMS2/HTRA1* risk alleles were significant ($p<0.001$ and 0.001, respectively).

What the findings mean

Drusen area and volume measurements were related to stage of non-advanced AMD and were greater for eyes classified with intermediate vs. early AMD. In addition, among eyes with the same AMD grade (early or intermediate), genetic risk was associated with a higher drusen burden. *CFH* score and *ARMS2/HTRA1* were both independently associated with perifoveal drusen area and volume compared with no measurable drusen.

When comparing the adjusted means of the drusen area and volume for *CFH* score and *ARMS2/HTRA1*, we found significant trends for drusen measurements increasing with the number of risk alleles for each variant. The trends persisted when both genes were adjusted for each other as well as when the baseline AMD grade was included as a covariate in the analysis. So results show that these two different genetic variants contributed independently to drusen burden.

The associations between advanced AMD and the *CFH* Y402H variant as well

as the intronic SNP in *CFH rs1410996* have been well documented. The biologic mechanisms underlying their effect on drusen accumulation, however, have not been fully explored. Our previous analyses reported that *rs1410996* had a stronger effect and *Y402H* a reduced effect when both were in the same model, suggesting that this intronic variant may be more strongly associated with AMD.^{3,4,17}

CFH negatively regulates the alternate complement pathway and dampens the excessive C3 convertase activated by either immune complex deposition or from pathogens or damaged cell surfaces. *CFH* risk variants are functionally less efficient at dampening this response, leading to heightened complement activity, which can lead to AMD-related pathology. It should be noted that SNPs in the genes *ARMS2* and *HTRA1* at the chromosome 10q26 locus are in very high linkage disequilibrium and functional studies are needed to determine which gene products lead to AMD pathology.²⁵

This advanced RPE analysis algorithm or a similar method may be useful to categorize AMD stage with greater precision and

ability to quantify measurements than clinical observation or photography. Higher-resolution OCT may reduce variability in OCT grading and enhance the application of the RPE analysis algorithm. Future studies will provide more information about the impact of genetic variants on drusen morphology.

We did not find a significant association between OCT-derived drusen measurement and the HDL pathway genes (*ABCA1*, *LIPC*, and *CETP*), although effect estimates followed the trend seen in a previous prospective analysis.^{13,14,20,26} The *CFH* and *ARMS2/HTRA1* genes were related to the transition from early to intermediate AMD based on color photographs,^{13,14} and were also associated with larger OCT-derived drusen measurements in this study.¹⁶

Bottom line

SD-OCT can quantify variation in drusen morphology in a way that is accurate and reproducible. Other AMD phenotypes detectable on OCT, including subfoveal fluid, retinal and choroidal thickness, retinal hyper-reflective foci and other drusen characteristics such as hyper-reflectivity and

Table 2. Associations between drusen area and volume and *CFH* and *ARMS2/HTRA1*

No. of Risk Alleles	n (eyes)	Univariate Gene Analysis*				Bivariate Gene Analysis†			
		Drusen Area Mean (mm ² ±SE)	p-value	Drusen Volume Mean (mm ³ ±SE)	p-value	Drusen Area Mean (mm ² ±SE)	p-value	Drusen Volume Mean (mm ³ ±SE)	p-value
<i>CFH</i> Risk Score‡									
0-1	39	0.07 ± 0.16	Ref	0.0002 ± 0.008	Ref	0.25 ± 0.17	Ref	0.007 ± 0.008	Ref
2	103	0.49 ± 0.10	0.03	0.019 ± 0.005	0.04	0.57 ± 0.11	0.09	0.022 ± 0.005	0.11
3-4	97	0.66 ± 0.10	<0.001	0.029 ± 0.005	<0.001	0.74 ± 0.11	0.01	0.032 ± 0.005	0.006
p (trend)	NA	NA	0.004	NA	0.002	NA	0.01§	NA	0.005§
<i>ARMS2/HTRA1: rs10490924#</i>									
0	105	0.194 ± 0.10	Ref	0.007 ± 0.005	Ref	0.15 ± 0.098	Ref	0.005 ± 0.0047	Ref
1	104	0.677 ± 0.10	<0.001	0.028 ± 0.005	0.002	0.60 ± 0.10	0.001	0.024 ± 0.005	0.004
2	30	0.898 ± 0.19	0.008	0.036 ± 0.009	0.004	0.80 ± 0.19	0.002	0.031 ± 0.0089	0.009
p (trend)	NA	NA	<0.001	NA	<0.001	NA	<0.001#	NA	0.001#

Key: * Analyses based on continuous area and volume, adjusting for age, sex, body mass index (BMI), smoking, disease grade and education. † Analyses for *CFH* score based on continuous area and volume, adjusting for age, sex, BMI, smoking, education, disease grade, and number of *ARMS2/HTRA1* risk alleles; analysis for *ARMS2/HTRA1* was performed similarly, adjusting for *CFH* score. ‡ Number of risk alleles for *rs1410996* and *rs1061170* combined. § P trend assessing effect on drusen measurements per 1 category increase in *CFH* score was obtained after adjusting for number of *ARMS2/HTRA1* risk alleles and other risk factors. # p trend assessing effect of increase in *ARMS2/HTRA1* risk alleles was obtained after adjusting for categories of the *CFH* score and other risk factors.

homogeneity, present opportunities for exploration in the context of subtyping AMD and assessing the risk of progression, as well as defining the associations with genetic variants. Further defining the relationship between disease severity, morphologic features, and genetic factors could enhance patient management and treatment as we move toward individualized precision medicine. ^{RS}

Contents of this paper were presented in part at the American Academy of Ophthalmology meeting, New Orleans, November 12, 2017, and Association for Research in Vision and Ophthalmology, Vancouver meeting, April 29, 2019.

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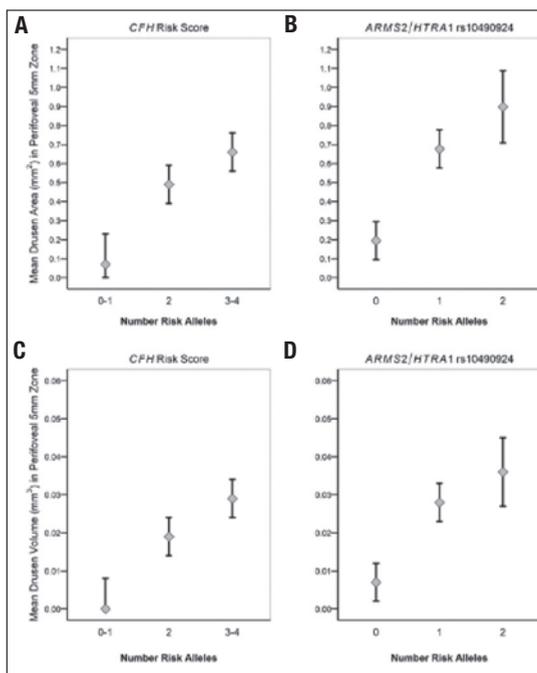


Figure 3. Independent associations between optical coherence tomography-derived perifoveal drusen measurements and number of risk alleles for drusen area for (A) CFH score and (B) ARMS2/HTRA1 SNP rs10490924 ($p=0.004$ and <0.001 , respectively); and drusen volume for (C) CFH score and (D) ARMS2/HTRA1 SNP rs10490924 ($p=0.002$ and <0.001 , respectively). The diamond represents the adjusted mean controlling for age, sex, smoking, body mass index, education and age-related macular degeneration grade. The vertical line represents plus or minus one standard error of the adjusted mean.

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Scleral windows for choroidal effusions

This procedure can improve uveoscleral outflow, but careful patient selection and management of expectations are important.

By Thomas A. Mendel, MD, PhD, Jessica L. Cao, MD, and Aleksandra V. Rachitskaya, MD



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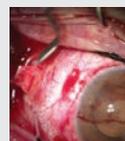
It's been hypothesized that in a patient with choroidal effusions, especially in the setting of nanophthalmos, the thickened sclera can compress vortex veins and lead to formation and persistence of choroidal effusions and serous retinal detachments. In these cases, scleral windows can increase uveoscleral outflow. For this procedure, careful patient selection with an appropriate discussion of prognosis and expectations is important because the serous retinal detachment usually improves gradually.

Starting the procedure

Exposure is crucial. After a conjunctival peritomy, all four rectus muscles are isolated and tied off with traction sutures. The nanophthalmic eye is notably smaller than what you might expect from scleral buckling.

The key to success is careful dissection of the scleral flap, beginning with an even-depth incision 4 to 5 mm in length parallel to the limbus and approximately 1 to 2 mm posterior to the muscle insertion. A 64- or 75-blade is well suited for this. Meticulous dissection approximately 4 to 5 mm posteriorly with a crescent blade then allows for flap creation.

View the Video



Watch as Drs. Mendel, Cao, and Rachitskaya perform scleral windows for choroidal effusions. Available at: https://bit.ly/VideoPearl_018

The sclera is significantly thickened in these cases. You need to establish the appropriate dissection depth. The goal is to see some graying of the remaining sclera, which indicates that it's appropriately thin. The flap is carried posteriorly and care should be taken not to damage the vortex veins. We prefer to leave the flaps attached posteriorly and amputate at the end of the case to minimize risk of intraoperative hypotony and to help with exposure if sclerectomies need to be enlarged further.

Incising the sclera

We use a 75-blade to incise the sclera radially in the middle of the dissected bed followed by Kelly punch-assisted sclerectomy to allow for drainage of choroidal fluid. We recommend enlarging the sclerotomy by rotating the punch 180 degrees.

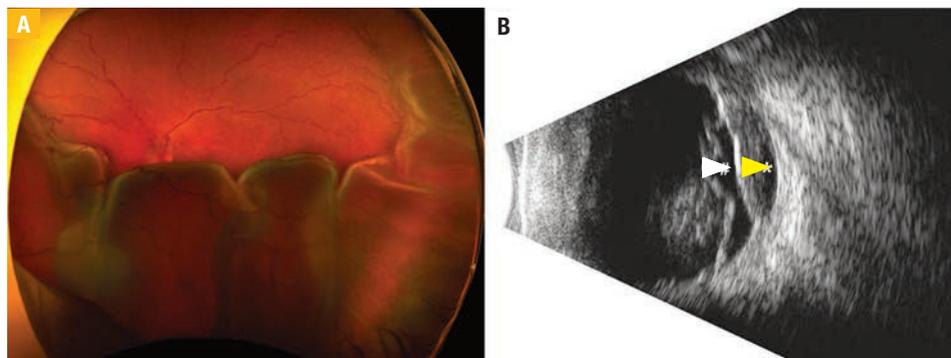
It's important to avoid intraoperative
(Continued on page 42)

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DISCLOSURES: Dr. Hahn has no relevant relationships to disclose.



Widefield fundus photograph (A) shows choroidal effusions and inferior serous detachment and B-scan ultrasound (B) at 6 o'clock shows choroidal effusion (yellow arrowhead) and subretinal fluid (white arrowhead).

When apathy is not an option

How retina specialists can approach societal issues and racial injustice on social media.

When we initially discussed this column, we had a general overview of the topics we wanted to cover, hopeful that they would be useful for both those just finding their social media identity to the more advanced users. This column's topic is not one we initially planned, but is arguably one of more significance than any other we'll explicate.

On May 25, George Floyd, a 46-year-old African American man, was killed when a Minneapolis police officer pressed a knee against his neck for more than eight minutes. Public outrage over his death quickly spread, unleashing protests of racial injustice across the United States and around the world since. A question I've received dozens of times goes something like this: Should I use my professional social media profile to comment on racial injustice or should I continue to focus on retina and medical topics?

What not to do

On the surface, this question may seem innocent and the answer may appear to align with guidance from the American College of Physicians and Federation of State Medical Boards: that physicians should separate their professional and personal identities to manage patient-physician boundaries online.¹

However, today this won't pass muster. Apathy is not an option. Professional silence is tantamount to enablement. To quote Boston University psychiatrist Michelle Durham, MD, MPH, "Professional silence in the face of social injustice is wrong ... To try to avoid the political fray through silence is impossible ... Either engage or assist the harm."²

Where do we stand?

To date, numerous medical societies have used social media to speak up. The American Academy of Ophthalmology has joined with other medical societies to advocate using our positive voice to speak out against injustice. I

believe we all want to be part of a professional society that doesn't tolerate hate crimes and discrimination.

It's appropriate for the public space

I've stated previously that you need to separate your professional platform from your personal views so as to avoid the dangerous pitfalls of patient privacy violation or unintended bias. This does not change.

However, one must comprehend that, as Matthew DeCamp, MD, PhD, and colleagues summarized in a recent *JAMA* editorial, a simpler approach for issues of social importance is one that asks physicians, not whether potential social media content is personal or professional, but whether it's appropriate for a public space.³

Issues of racial injustice are appropriate for the public space. Moreover, public discourse is exactly what's needed to ferment sentiment into action that translates into progress.

Ultimately, as physicians, our central goal is to care for others. We must act upon factors that threaten health, whether pathophysiological or societal. Racism, violence and prejudice cannot be tolerated, and remaining silent, falsely protecting oneself in a cloak of apathy, will not suffice.

So, I urge you to use your social media profile to speak. Do it eloquently. Do it forcefully. Do it directly. Avoid derogatory remarks. Avoid insults. Avoid provocations—but realize that if you believe your social media is part of your voice, you must speak up because apathy is not an option. 

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Scleral windows for choroidal effusions

(Continued from page 40)

hypotony. Maintain intraocular pressure by pulling on the sutures around the rectus muscles. After each egress of choroidal fluid, adjust the intraocular pressure as needed with balanced salt solution injected into the anterior chamber with a 30-gauge needle.

We typically perform scleral windows in all four quadrants if feasible. Note that with a very thick sclera, the blades can dull; you may need more than one in a case. At the end of the case after careful inspection, the flaps are removed and the conjunctiva is reapproximated at the limbus. **RS**

Has the time come for AMD home monitoring?

(Continued from page 27)

An aid for the ‘new normal’

We’re still trying to navigate “normal” office procedures in the wake of COVID-19. This may include limiting in-office imaging. However, devices that give us the flexibility to monitor patients remotely allow us to stay connected with them and ensure we are still providing the highest quality care when they need to be in our offices.

Remote diagnostic clinics providing monitoring services, including compliance of home use of the device, are important partners in patient comanagement in this new era. Also, in this model we can hand off time-consuming patient education tasks of how to utilize the system to the phone service of a remote provider, reducing the time a patient spends in our clinics.

At the same time, the ability to remotely review images by retina specialists could allow us to engage directly with our patients on telehealth consultations. Extreme times such as these require innovative thinking and adaptability to provide the best care. Technologies such as Home OCT may help us to do so as we move forward. If all goes well, the remote monitoring service is ex-

pected to be available in the United States by prescription in the first half of 2021. **RS**

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Long-term anti-VEGF effect

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