A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA® SPECIALIST

VOL. 9, NO. 5 • SEPTEMBER/OCTOBER 2024

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Telehealth in RETINA

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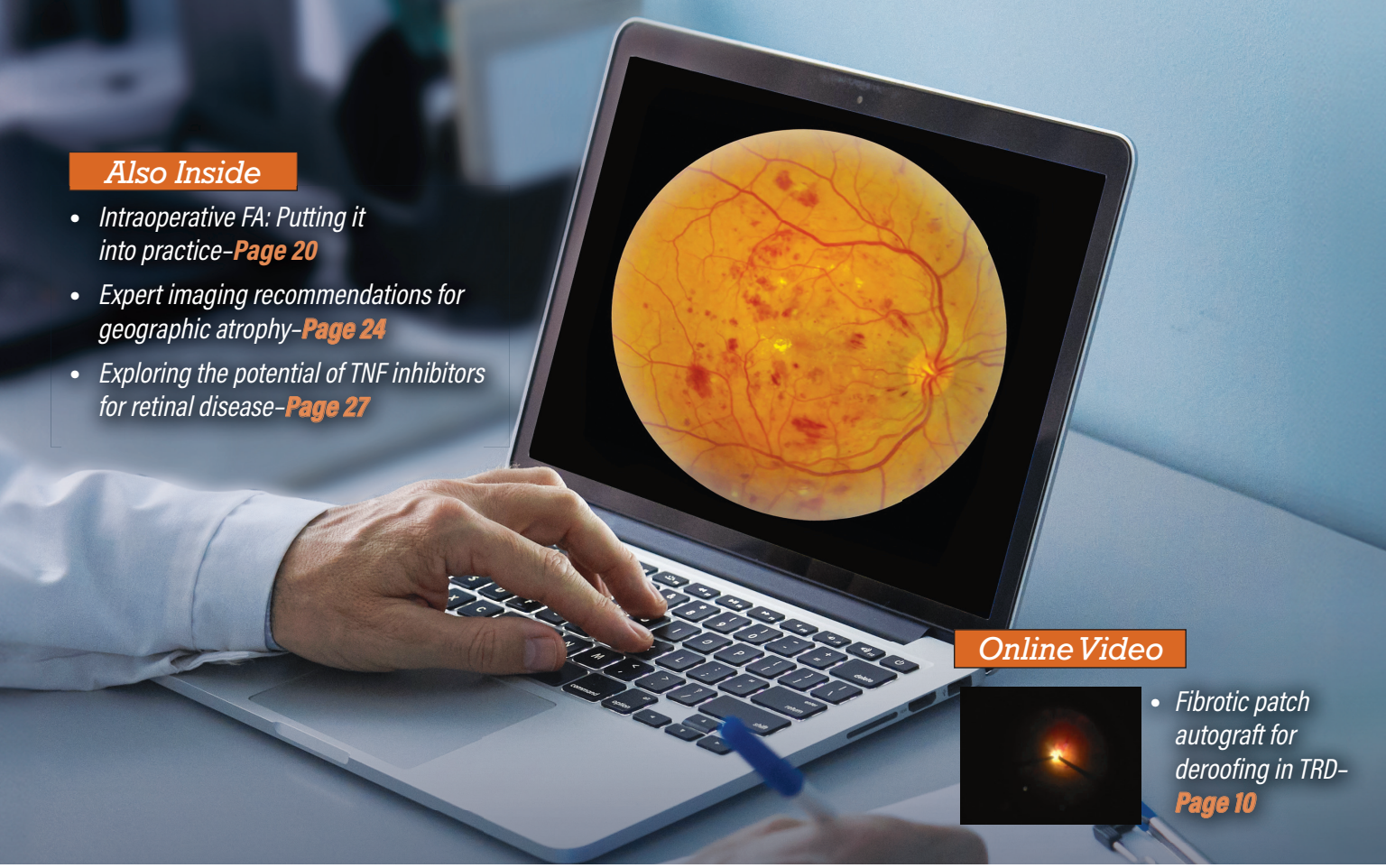

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izervay™
(avacincaptad pegol intravitreal solution) 2 mg

DETECT GA BEFORE YOUR PATIENTS DO

By the time geographic atrophy (GA) is obvious, the damage is done.[1,2] Keep GA on your radar because the earlier you can detect it, the sooner you can mitigate its effect with IZERVAY.[3]

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INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

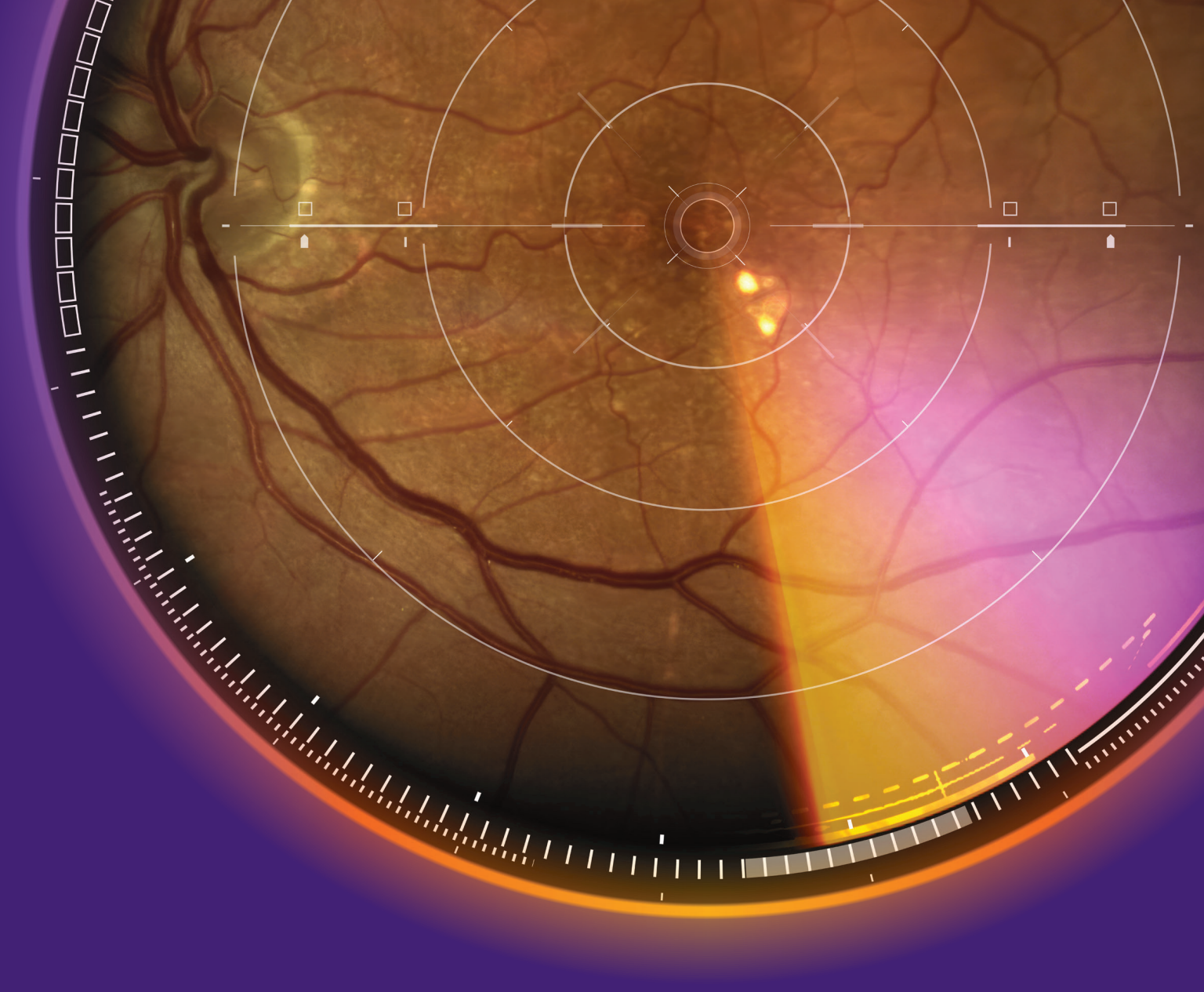
WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.



Increase in Intraocular Pressure

- Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

Please see Brief Summary of Prescribing Information for IZERVAY on the following page.

Image courtesy of Dr. Julie Rodman.

References: 1. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology*. 1997;104(10):1677-1691. **2.** Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369-390. **3.** IZERVAY™. Package insert. Northbrook, IL: Astellas Pharma US, Inc.

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 800-707-4479.

1 INDICATIONS AND USAGE

IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage

The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

IZERVAY is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD

In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS

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

- Ocular and periocular infections
- Neovascular AMD
- Active intraocular inflammation
- Increase in intraocular pressure
- Endophthalmitis and retinal detachments

6.1 Clinical Trials 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.

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred Vision*	8%	5%
Choroidal neovascularization	7%	4%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data

An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, or the effects of the drug on the breastfed infant or on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IZERVAY and any potential adverse effects on the breastfed infant from IZERVAY.

8.4 Pediatric Use

Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

Distributed by: Astellas Pharma US, Inc.
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US-AP-2400227 07/24

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EDITORIAL

By Jason Hsu, MD

Waste not, want not

For the last few decades, there has been increasing awareness about the environmental impacts of plastics and waste products. More efforts have been made to encourage recycling and make it readily available.

However, at the same time, ophthalmologists, including us vitreoretinal surgeons, have witnessed an increase in the use of disposables. It's relatively rare these days that we use any instrumentation that's reusable. While our instruments are relatively small, we have to consider the packaging, too, which often accounts for a comparable if not greater amount of the medical waste than the instrument itself. This may even be more so in our offices, with many of the injectables and their associated packaging.[1]

While it's easy to think that we're only a small piece of a much larger puzzle contributing to waste, I was shocked to hear that health care in the United States has been estimated to be responsible for nearly 9 percent of greenhouse gas emissions, which, in turn, are catapulting us toward a cycle of climate change and worsening health conditions.[2]

Much of these emissions emanate from the manufacturing and distribution of single-use surgical and medical supplies. On one hand, single-use disposables are certainly convenient and provide consistency. No more worries about damaged reusable instruments and the associated headaches of cleaning and sterilizing between cases. Perhaps, there's a theoretical advantage in infection control with single-use supplies, but this has not been consistently borne out in studies.

So what can we do? First, we can encourage sorting of waste and maximizing recycling efforts. As consumers of these disposable products, another important tool is advocacy, especially with manufacturers and product representatives to design supplies and instruments that use more sustainable materials and minimize the associated packaging. Perhaps it's time for us to revisit the concept of reusable instruments, which not only improves sustainability but will also likely result in cost savings.

Other ideas include standardizing equipment use across surgeons in a given center, thereby reducing unused supplies which may expire and be discarded. In that same vein, try only to open things that are absolutely needed for each case. Work with your OR to design custom packs that only contain the supplies that are always used. Consider choosing items that use less material, such as a sterile face drape rather than a full body drape.

When we step back, the vast majority of us will agree that healthcare waste is excessive in the United States.[3] It's time to fight inertia and act. Our actions today, no matter how trivial they seem, will cumulatively allow for a better tomorrow.

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2. Sherry B, Lee S, Ramos Cadena MDLA, et al. How ophthalmologists can decarbonize eye care: A review of existing sustainability strategies and steps ophthalmologists can take. *Ophthalmology*. 2023;130:702-714.
3. Oydanich M, Khouri AS. The environmental and economic burden of surgical waste in ophthalmology operating rooms. *Eye Lond Engl*. 2024;38:822-823.

A PUBLICATION BY REVIEW of OPHTHALMOLOGY
RETINA SPECIALIST
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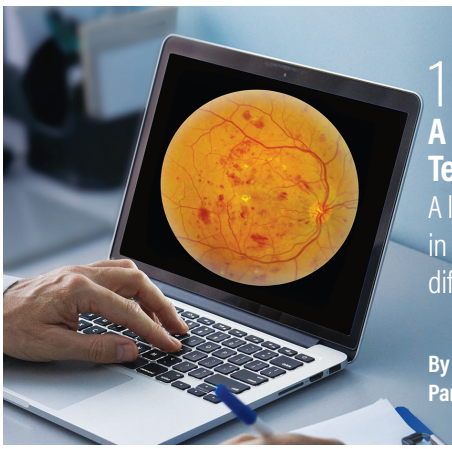
FEATURES



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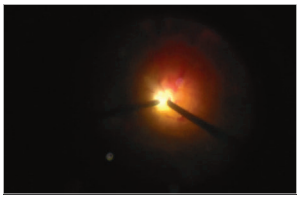

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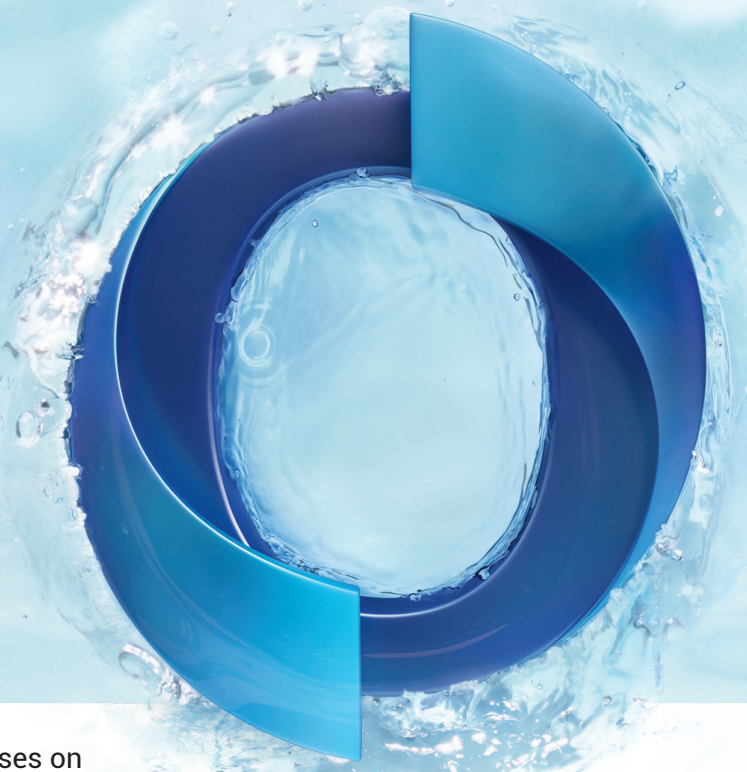

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IHEEZO™ is the topical ocular anesthetic that compromises on nothing. Rapid onset and an established safety profile for your patients. No uncertainty with a sterile, single-use unit for you.

In a Phase III clinical study of IHEEZO,

NO supplemental treatment needed to maintain anesthesia*†[1]

NO serious adverse events with an established safety profile[2]

NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

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References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

IHEEZO™

(chloroprocaine HCl ophthalmic gel) 3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials 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.

The data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

The safety and effectiveness of IHEEZO have not been established in pediatric patients.

8.5 Geriatric Use

No overall differences in safety or effectiveness of IHEEZO have been observed between elderly and younger patients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

For Full Prescribing Information, please visit www.iheezo.com/prescribinginformation.

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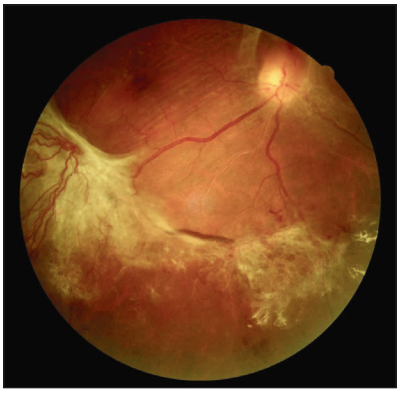
Combined Treatment for PDR: Sequence Matters

Initial treatment of patients with proliferative diabetic retinopathy often involves a combined approach using panretinal photocoagulation and anti-VEGF injections. Large randomized clinical trials usually prefer monotherapy, limiting the information available on the outcomes of combined treatment approaches and whether the sequence of PRP and anti-VEGF therapy has an effect. A new study published in *JAMA Ophthalmology* aimed to close this research gap by comparing the need for pars plana vitrectomy among patients treated with PRP first then anti-VEGF injections and vice versa.

The retrospective cohort study included more than 3,000 patients with new PDR diagnoses from the TriNetX EHR network, stratified by therapy with PRP and subsequent anti-VEGF or anti-VEGF and subsequent PRP. While the primary outcome was the need for PPV, secondary outcomes included incidence of PPV, vitreous hemorrhage or tractional retinal detachment. After propensity score matching, which controlled for baseline demographic characteristics and medical comorbidities, there were 1,377 patients in each of the two treatment groups. The average age was 63 years in both groups, and the sex ratio was nearly 50:50.

The results showed that patients in the PRP-first group demonstrated a higher risk of needing PPV over the course of five years compared to those in the anti-VEGF-first group, with similar associations at six months, one year and three years. This group also had higher rates of vitreous hemorrhage and tractional retinal detachment at the same four time points.

"While combined therapy for the treatment of PDR has gained popularity in clinical practice, as shown by the ASRS PAT surveys, if this study's approach is considered, it is unknown if the order of treatment modalities affects outcomes," the researchers explained in their paper. They cited one previous study that found "PRP after intravitreal conbercept injections (Lumitin; Kanghong Biotechnology) was associated with a reduced number of subsequent anti-VEGF injections compared with eyes treated with PRP before intravitreal conbercept at two years [six vs. 8.5 injections], despite no difference in visual and anatomic outcomes between cohorts."



Furthermore, in the present study, which used a large, heterogenous, real-world database of matched patients with PDR, "administration of PRP first was associated with an increased risk of undergoing PPV, as well as developing vitreous hemorrhage and tractional retinal detachment, compared with anti-VEGF injection [first]," the study authors wrote.

Study co-author Amer Fadel Alsoudi, MD, has some thoughts on what's behind the results. "Combined treatment is preferred practice among ophthalmologists across the world (supported by ASRS PAT surveys and real world practice)," he says, "with some evidence to support better outcomes than monotherapy (though no study that directly compares combined treatment with monotherapy). We recently published that monotherapy anti-VEGF may have improved outcomes than monotherapy PRP in a select cohort of patients. It's perhaps the VEGF sequestration with anti-VEGF therapy that facilitates successful PRP and prevention of PDR complications."

While the literature on this topic is growing, they caution that further research is still warranted to determine the optimal order of PRP and anti-VEGF injections for treating PDR, especially considering the increasing popularity of this combined approach.

Dr. Alsoudi notes what actualy surprised him about the results. "[I was surprised by] the magnitude of difference regarding outcomes secondary to the order of treatment that remained significant at every time point observed," he says. "When we ask questions in science, we often don't expect results that support or reject our hypothesis—rather to better inform the public one way or the other. When we find a signal that hasn't been explained yet, we're surprised.

In terms of limitations, Dr. Alsoud notes that, "Without belaboring the point, de-identified large database studies that require accurate clinical coding are limited by the possibility of inaccurate coding—though physician compensation is reliant on accurate coding."

REFERENCE

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Fibrotic patch autograft for deroofing in TRD

One approach to management of an unexpected and challenging case of foveal deroofing in tractional retinal detachment.

By Miguel Cruz Pimentel, MD, Tina Felfeli, MD, PhD, and Efrem D. Mandelcorn, MD, FRCSC

Miguel Cruz Pimentel, MD

Tina Felfeli, MD, PhD

Efrem D. Mandelcorn, MD, FRCSC

Taut neovascular fibrotic membrane caused by regressed neovascularization is common in patients with tractional retinal detachment.[1] Retinal fibrosis can be present in two variations, fibrovascular and avascular.

Müller cells play an essential role in the development of retinal fibrosis. As a response to chronic stress, these cells undergo massive gliosis.[1,2] When neovascularization is located near the fovea,[3] there's a risk of intraoperative deroofing of the fovea, leading to a macular hole with irregular edges.

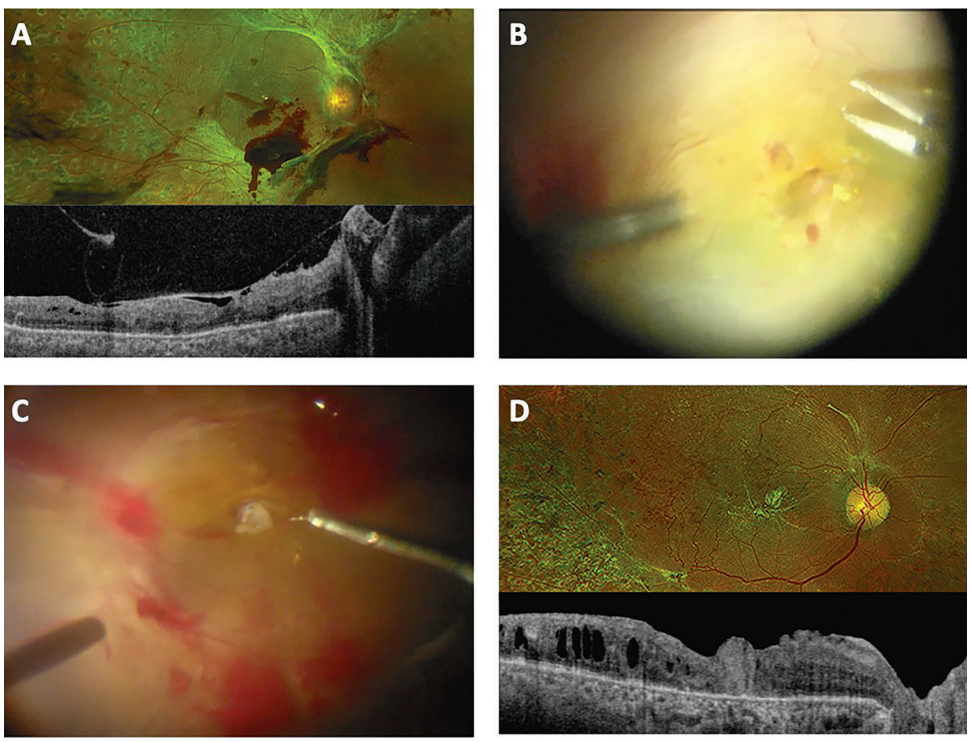
In such cases, attempting an internal limiting membrane peel with or without an inverted flap is always a good option.

View the Video

Watch as Dr. Cruz Pimentel, Dr. Felfeli and Dr. Mandelcorn create a fibriotic patch autograft to repair a complex tractional diabetic retinal detachment. Go to bit.ly/VideoPearl-42 or scan the QR code.

However, peeling the ILM can be difficult because of subretinal fluid in long-standing retinal detachment. An amniotic

(Continued on page 15)



A) Preoperative optical coherence tomography of a patient with complex tractional diabetic retinal detachment in the right eye. B) A large intraoperative macular tear was inadvertently created while removing foveal attachments of regressed fibrotic tissue. C) A patch of regressed retinal fibrosis was used as a graft to plug the macular tear. D) At two months postoperatively, the patient had relatively good anatomical and functional outcomes with complete macular hole closure without a central scotoma and a visual acuity of 20/400.

BIOS

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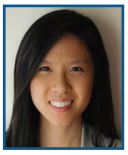
DISCLOSURES: The authors have no relevant disclosures.

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

Differentiating between the placoid chorioretinitis conditions

Become an expert at picking out the diagnostic clues.

By Julia Xia, MD, and Lynn Hassman, MD, PhD



Julia Xia, MD

Lynn Hassman, MD, PhD

Placoid chorioretinitis refers to a group of inflammatory clinical conditions that have some signs and symptoms in common, but also have unique aspects as well. Discerning these differences is key to a proper diagnosis. Here, we'll describe the different conditions and how to tell them apart.

The spectrum of conditions

The conditions that make up the spectrum of placoid chorioretinitis share a common characteristic of having focal areas of retinal plaques that typically involve the outer retina and retinal pigment epithelium as well as the underlying choriocapillaris. These conditions include acute posterior multifocal placoid pigment epitheliopathy (APMPPE), persistent placoid maculopathy (PPM) or macular serpiginous choroiditis, relentless placoid chorioretinitis (RPC) or ampiginous chorioretinitis; serpiginous choroiditis (SC), serpiginous-like choroiditis (SLC) associated with tuberculosis, and acute syphilitic posterior placoid chorioretinitis (ASPPC).

These conditions can be associated with infectious or autoimmune diseases or occur without systemic disease. The predominant mechanism is thought to be inflammation that causes hypoperfusion of the choriocapillaris resulting in ischemia to the overlying RPE and outer retina with eventual chorioretinal atrophy.[1]

Patients typically present with acute painless blurred vision, photopsia, metamorphopsia, scotomas or floaters. Patients may sometimes have a viral prodrome in APMPPE, RPC or PPM. They can also rarely have neurologic symptoms such as a headache which should raise suspicion for cerebral vasculitis that can be associated with APMPPE, PPM or RPC. They may also have a skin rash or genital lesions consistent with syphilis, and asking about sexual or travel history and sick contacts may help elucidate risk factors for syphilis or TB.

Clinical findings

The size and distribution of the placoid lesions can often help differentiate between the different entities. APMPPE typically manifests as larger (1 to 2-disc areas) creamy white lesions at the level of the RPE that are limited to the posterior pole, while RPC can involve smaller lesions (about half a disc area in size) that become greater in number with disease progression and can spread to involve the periphery.[2] PPM typically presents as bilateral, foveal-centered lesions.[3] Lesions in SC appear as gray-white lesions that project in a continuous geographic "serpentine" manner from the optic nerve *(Figure 1A)*.[4] TB-associated SLC lesions, on the other hand, can involve the posterior pole and periphery and may not involve the peripapillary area until late in the disease. Additionally, serpiginous-like choroiditis lesions can be multifocal as op-

Key treatment considerations for placoid chorioretinitis:

1. Rule out syphilis, tuberculosis and sarcoidosis.
2. Ask about neurologic symptoms and, if present, obtain urgent CT or MR angiography to rule out CNS vasculitis.
3. Cases related to tuberculosis or syphilis require antibacterial therapy and may also require corticosteroids.
4. Treat all foveal or optic-nerve threatening lesions with corticosteroids.
5. While APMPPEE doesn't usually recur, most other placoid chorioretinitis is chronic/progressive and requires long-term steroid-sparing immune suppression.
6. Foveal and macular lesions are at risk for CNV, requiring anti-VEGF therapy.

BIOS

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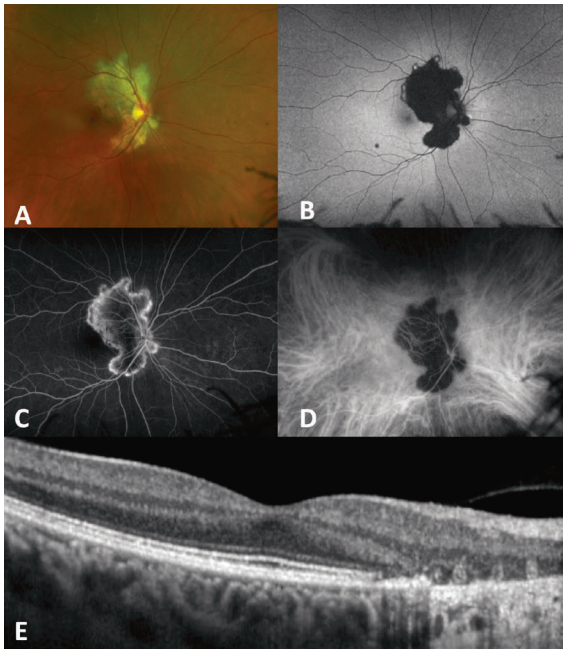


Figure 1. Serpiginous choroiditis. A) Fundus photo shows a gray-white geographic lesion extending from the optic nerve. B) Fundus autofluorescence shows hyperautofluorescence at active areas of the lesion with hypoautofluorescent center where disease is currently inactive. C) Fluorescein angiography shows late hyperfluorescence of lesion edges. D) Indocyanine green angiography shows hypoautofluorescence throughout the lesion. E) Optical coherence tomography shows disruption of the ellipsoid zone and outer retina, as well as atrophy of the retinal pigment epithelium.

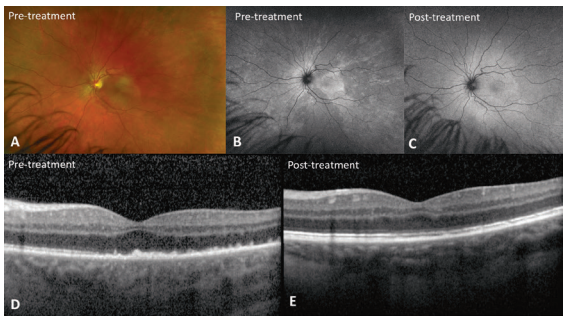


Figure 2. Acute syphilitic posterior placoid chorioretinitis. A) Fundus photo shows a yellow placoid lesion in the macula. B) Fundus autofluorescence demonstrates hyperautofluorescence corresponding to the placoid lesion that resolves after treatment with intravenous penicillin (C). D) Optical coherence tomography shows punctate spots in the choroid, ellipsoid zone disruption, and a nodular appearance of the retinal pigment epithelium that are restored after treatment (E).

posed to spreading continuously, like in SC, and are usually accompanied by more significant anterior or vitreous inflammation compared to SC.[5,6] Acute syphilitic posterior placoid chorioretinitis typically presents as a subtle yellow whitening of the macula with marked inflammation of the vitreous and anterior chamber *(Figure 2A)*[7] unless the patient is immune-compromised.

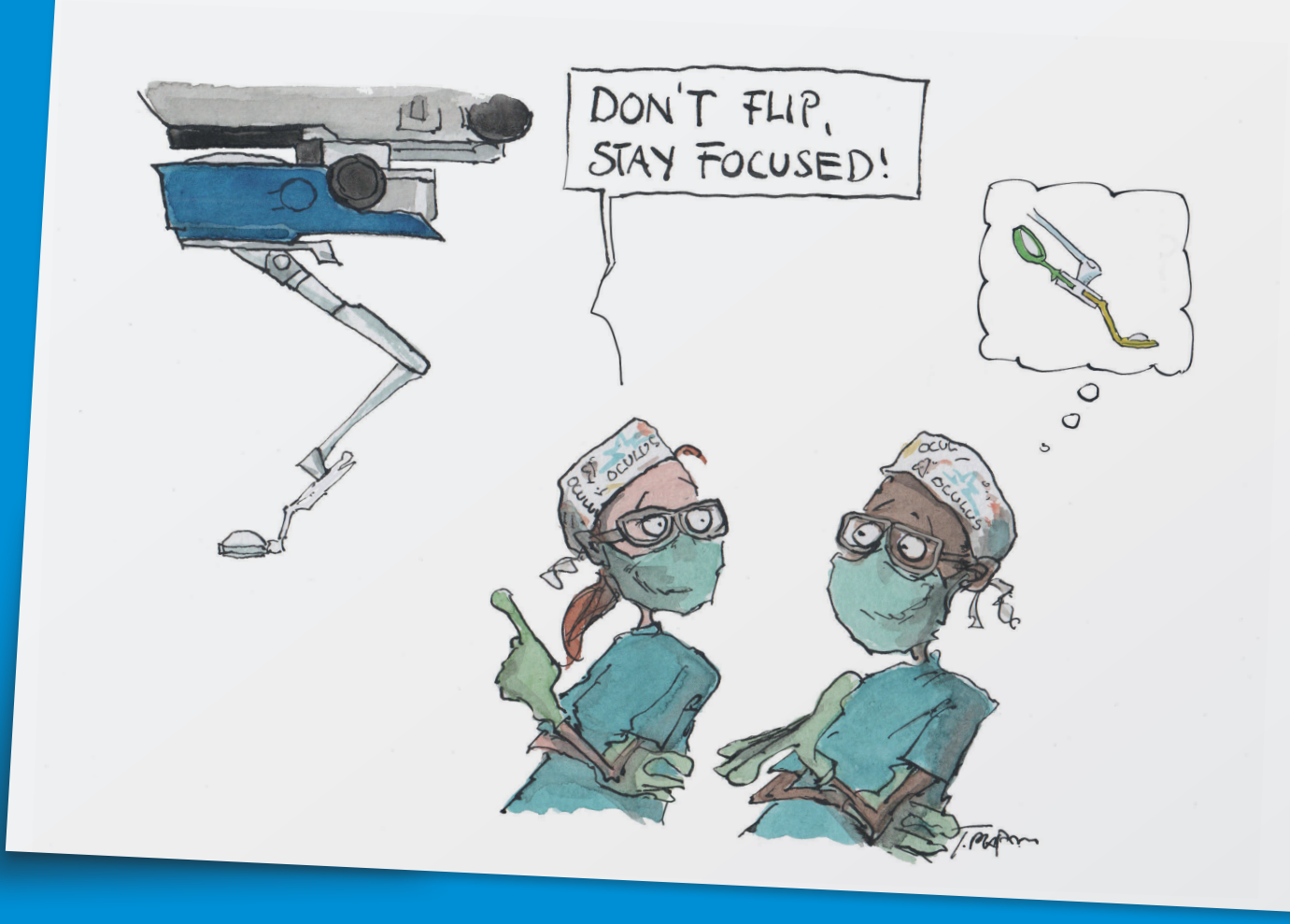
The clinical course is also important in differentiating the various placoid conditions. APMPPE is usually acute, monophasic and self-limited. PPM may also present acutely but usually progresses to foveal atrophy without treatment and has higher rates of choroidal neovascularization.[8] RPC, on the other hand, has an aggressive clinical course with long periods of disease activity, can relapse over months to years and requires treatment *(Figure 3)*. SC may be initially symptomatic if the lesion starts outside the macula but is a progressive condition that also requires long-term therapy.

Imaging findings

Multimodal imaging can be useful for detecting more lesions than may be clinically apparent and can also help evaluate disease activity. The different placoid entities share some common imaging features that can help differentiate them from other inflammatory chorioretinal disorders. Fundus autofluorescence can show hyperautofluorescence at the edges of active lesions *(Figure 3B)* that can also have hypoautofluorescent halos in SC *(Figure 1B)*.[9,10] Placoid lesions on FAF will generally transition from hyperAF to hypoAF once lesions become inactive, however areas of RPE hyperplasia or scarring may remain hyperAF. Fluorescein angiography shows early hypofluorescence and late hyperfluorescence of the lesions, especially at the edge of an active lesion *(Figure 1C)* or in areas of scar or chorioretinal atrophy.[11]

OCTA demonstrates hyporeflective areas of perfusion deficits at the level of the choriocapillaris in active disease.[18-23] OCTA studies suggest that FAF lesions may lag behind choriocapillary flow voids seen on OCTA.[19] Indocyanine green angiography shows early and late hypofluorescence corresponding to placoid lesions due to choroidal ischemia *(Figure 1D)* which may partially or completely resolve or persist with disease inactivity.[12,13]

Optical coherence tomography through active placoid lesions shows increased choroidal thickness, hyperreflective disruption of the ellipsoid zone in all cases and variably of the outer nuclear layer and retinal pigment epithelium. Ultimately, there can be recovery of the outer retinal layers in conditions like APMPPE or syphilitic chorioretinitis after treatment. However, in conditions like SLC and RPC, placoid lesions tend to transition to outer retinal atrophy and photoreceptor loss in the in-



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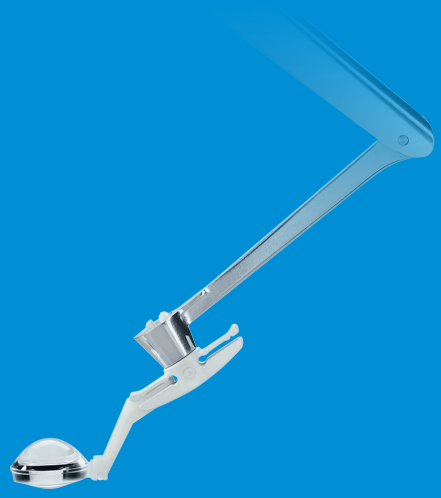

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Key Imaging Features of Placoid Chorioretinitis

	Active Lesions	Healed Lesions	Scarred Lesions
Fluorescein angiography	Early hypofluorescence, late staining	May resolve OR persistently stain	Staining
Indocyanine green angiography	Hypofluorescence	May normalize OR have persistent hypofluorescence	Persistent hypofluorescence
Fundus autofluorescence	Hyperautofluorescence May have central hypofluorescence	May normalize OR have milder hyperautofluorescence OR hypo-autofluorescence	Hyperautofluorescence
Optical coherence tomography	Hyperreflective disruption of the ellipsoid zone, +/- outer nuclear layer hyperreflectivity, +/- RPE disruption	May resolve (APMPPE) OR have persistent outer retinal atrophy (PPM, SC), May have subretinal fibrosis OR retinal cysts (SC)	May have persistent hyperreflective RPE OR atrophy of RPE, outer retinal and choroid

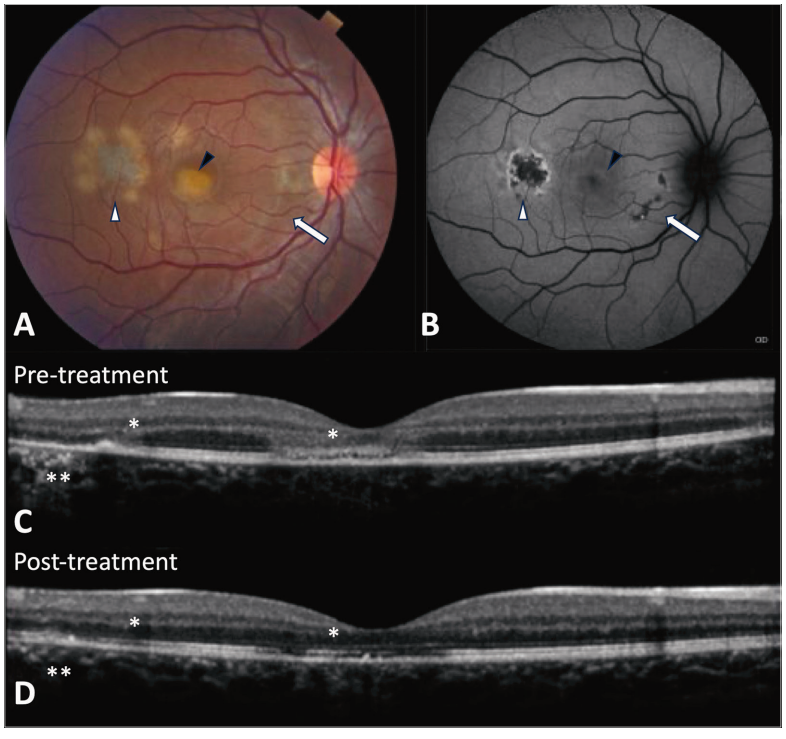

Figure 3. Relentless placoid chorioretinitis (RPC). A) Fundus photo shows creamy yellow/white lesions at the level of the retinal pigment epithelium in the posterior pole that was initially diagnosed as acute posterior multifocal placoid pigment epitheliopathy. However, this patient later returned with new lesions suggesting a diagnosis of RPC. B) Fundus autofluorescence shows a new active lesion in the temporal macula with hyperautofluorescent edges (white arrowhead) and fovea with subtle hyperautoflouresence (black arrowhead) and healed lesions (arrow) that are hypoautoflourescent and minimally apparent on the fundus photo. C) Optical coherence tomography shows hyperreflective disruption of the ellipsoid zone and outer nuclear layer (asterisk) as well as attenuation and hyperreflectivity of the retinal pigment epithelium (double asterisk) that partially recover after treatment with immunosuppression (D).

active stages of the disease *(Figure 1E)*.[9,14-16] The OCT findings that are specific to ASPPC include punctate hyper-reflective spots in the choroid and nodular appearing RPE *(Figure 2D)*.[17]

Diagnosis

Diagnostic workup to differentiate between infectious and autoimmune etiologies is imperative to determine the correct therapeutic approach. Infectious causes of placoid chorioretinitis include primarily syphilis, TB and possibly coxsackievirus. Less common pathogens include *Histoplasma*, Group A streptococcus, adenovirus type 5 and *Borrelia* (Lyme disease). Autoimmune diseases associated with placoid chorioretinitis can include sarcoidosis *(Figure 4)*, cerebral vasculitis, ulcerative colitis, granulomatosis and polyangiitis. Labs should, at a minimum, include RPR, QuantiFERON Gold and chest X-ray. Clinical evaluation should include a careful review of systems for further targeted testing or subspecialist referral. Any patient with placoid lesions and neurological symptoms, including new or unusual headaches, should undergo urgent neuroimaging to evaluate for cerebral vasculitis that can be associated with APMPPE, PPM and RPC.

Treatment

Treatment of infectious placoid chorioretinitis is targeted at the underlying infection with generally good resolution and visual outcomes afterward. Syphilitic chorioretinitis requires treatment with 10 to 14 days of intravenous penicillin, which leads to the resolution of abnormal autofluorescence (*Figure 2C*) and restoration of the RPE and outer retina on OCT *(Figure 2E)*.[17] Placoid chorioretinitis associated with TB or pulmonary histoplasmosis requires anti-TB and anti-fungal therapy, respectively, and may also require adjunctive steroid therapy to control inflammation.

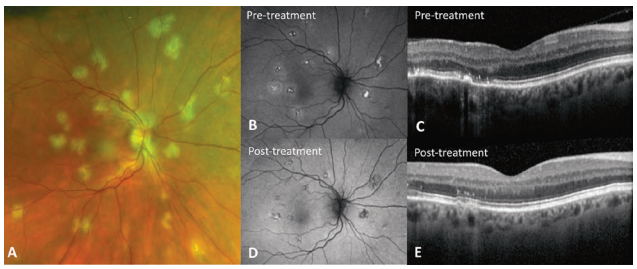

Figure 4. Placoid chorioretinitis associated with neurosarcoidosis. A) Fundus photo shows multiple creamy white placoid lesions in the posterior pole. B) Fundus autofluorescence shows mixed hypo and hyperfluorescent areas corresponding to the placoid lesions. C) Optical coherence tomography shows hyperreflective disruption of the ellipsoid zone, outer nuclear layer and retinal pigment epitheliaum. D) Fundus autofluorescence shows decreased hyperautofluorescence with restoration of the ellipsoid zone on OCT (E) after treatment with intravitreal steroid and systemic immunosuppression.

Self-limiting conditions like APMPPE may not always require treatment,[24] but vision-threatening lesions should be treated. Outside of APMPPEE, other forms of non-infectious placoid chorioretinitis are usually aggressive, requiring immunosuppression with steroid therapy first, which can be in the form of systemic steroids or local injections. Patients with recurrent disease are then escalated to steroid-sparing immunosuppression.

Outcomes

Visual outcomes are quite favorable, as outer retinal irregularities improve with treatment *(Figures 3 and 4)*, but final visual acuity also depends on the location and degree of retinal atrophy that can remain after disease activity subsides.[24] Complications such as choroidal neovascularization are higher in PPM and SC than in other types of placoid chorioretinitis and may warrant anti-VEGF therapy.[25,26]

Bottom Line

Placoid chorioretinitis can have many etiologies, ranging from infectious to autoimmune. Clinical findings, disease course and laboratory work-up can help differentiate between different placoid entities. Treatment of infectious placoid conditions are targeted at the underlying infection while non-infectious etiologies can require a combination of steroid and immunosuppressive agents. RS

For a version with the full list of references, please see the online article at retina-specialist.com.

Fibrotic patch autograft for deroofing in TRD

(Continued from page 10)

membrane could be an alternative, but it may not be readily available in the operating room during the complication.

A retina autograft may also be an alternative, but it requires creation of a second retinal break in an eye that has active proliferation, which can lead to recurrent retinal detachment and proliferative vitreoretinopathy.

Our case

In this case, a 60-year-old female with type 2 diabetes presented with a complex tractional diabetic retinal detachment in the right eye. We advised surgery, but the patient didn't return for three months, and the TRD worsened. Visual acuity had deteriorated to hand motion.

Intraoperatively, while removing foveal attachments of regressed fibrotic tissue, we noted a macular tear with ragged edges caused by deroofing of the fovea during surgery.

We made an initial attempt to peel the ILM, but subretinal fluid and complex exudates made creating an ILM-inverted flap impossible. We deliberately left a residual patch of regressed retinal fibrosis without delamination prior the fluid-air exchange to serve as a macular plug.

After completing the removal of the peripheral vitreous, and using ILM forceps to delicately dislodge the fibrosis patch, which was deliberately left tethered at its attachment site, we placed this fibrotic neovascular patch to plug the macular tear. Postoperatively, the patient had a complete macular hole closure without central scotoma. Visual acuity was 20/400 at the two-month follow-up.

Bottom line

This case highlights the use of regressed neovascular tissue as a solution for intraoperative management of macular holes caused by deroofing during TRD surgery. In cases where an unanticipated macular hole forms and no prepared amniotic membrane graft is available to close the macular tear, fibrotic neovascular membranes can be used to achieve anatomical closure. RS

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A state of stagnation: Telehealth in retina

A look at the potential of telehealth in retina and why achieving it is so difficult.

By Zaheer Coovadia, Shreya Shah and Ravi Parikh, MD, MPH


Zaheer Coovadia


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Bios

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DISCLOSURES: **Mr. Coovadia** and **Ms. Shah** have no relevant disclosures.

Dr. Parikh disclosed financial relationships with Anthem Blue Cross and Blue Shield, Apellis Pharmaceuticals, Regeneron Pharmaceuticals, GLG, Health and Wellness Partners, and Axon Advisors, and receives funding from the American Academy of Ophthalmology for work with the Relative Value Update Committee.

Take-home points

- The COVID-19 public health emergency highlighted ophthalmology's limited ability to conduct effective synchronous telehealth visits.
- The burden of vision-threatening retinal disease is growing, but effective treatments to prevent severe vision loss do exist. To best identify and treat these patients, the health-care system's delivery of care needs to be re-engineered using tools such as artificial intelligence-based detection and remote monitoring.
- AI-based imaging can make management of neovascular age-related macular degeneration more practical by immediately identifying recurrence of exudation with home-based optical coherence tomography. AI-based imaging can also allow for earlier detection of diabetic retinopathy using fundus photography.
- Cost, decreasing insurance reimbursements, and regulatory workflow/challenges limit the potential and adoption of AI in retinal diseases.

In the 1950s, one of the first uses of telemedicine happened at the Nebraska Psychiatric Institute and Norfolk State Hospital where patients received psychiatric evaluations through closed circuit television.[1]

Technology has since advanced a tremendous amount, opening up new methods of communication and consequently new ways of patient-doctor interaction. With the smart phone and applications such as Skype, FaceTime and Zoom, physicians have become much more accessible to patients.

But has this accessibility been taken advantage of? And what do these new forms of communication mean for the remote practice of ophthalmology? Up until the recent COVID-19 pandemic, video calls weren't often used in synchronous visits, with most physicians opting for communication via telephone. However, after the public health emergency, the telehealth landscape changed considerably.[2]

Here, we consider the current state of artificial intelligence utilization and teleophthalmology across two important retinal pathologies: diabetic retinopathy and age-related macular degeneration. Although both diseases have reliable and effective treatments, many patients, for a host of reasons, don't get adequate care. AI and telemedicine will be key to bringing these patients into care to prevent debilitating vision loss.

Telehealth takes off during lockdown

COVID-19 lockdowns were, understandably, disruptive. Follow-up appointments were missed, surgeries were canceled and emergency rooms swelled to capacity. Doctors scrambled to master new modalities, attempting to reach patients through phone or video chats.

Despite the history of telemedicine being used for DR, ophthalmologists used tele-

medicine the least at the beginning of the COVID-19 crisis. One study of teleophthalmology visits during the initial COVID lockdowns (March to May 2020) found that ophthalmology both experienced the greatest decline in visits (down to 23 percent of prepandemic rates) and produced the lowest proportion of tele-visits to total visits—about 7 percent compared to 76 percent in neurosurgery, the highest among specialties.[3]

The 2021 COVID-19 and Utilization of Teleophthalmology (CUT) Group study of office visits from September 2019 to September 2020 highlighted corneal and external disease conditions as the largest proportion of teleophthalmology visits (48 percent of all such visits), and retina/vitreous conditions and glaucoma with the smallest share, at 16.8 and 13.4 percent, respectively.[4]

The high proportion of anterior consultations is somewhat expected when we observe that chalazia made up 9.4 percent of all teleophthalmology claims and can be diagnosed via video.[4]

Ophthalmology wasn't ready

At its core, the CUT study showed that ophthalmology wasn't prepared for real-time telemedicine. Although asynchronous visits have long been standard in teleophthalmology with physicians classically using the store-and-forward method—interpreting scans remotely or after the patient has left—a synchronous visit is logistically more complicated.

A patient would need to have access to some type of remote slit lamp to perform live ophthalmoscopy—technology that's more advanced than that which is currently available to diagnose a condition in real time. Clearly, technological advances are needed to allow ophthalmologists to complete a more comprehensive synchronous ophthalmic exam/evaluation.

AI and telemedicine in DR

Proper use of telemedicine could increase the pool of people being seen by both increasing appointment efficiency and providing greater access to those not currently being monitored for retinopathy.

Some primary-care clinics have started experimenting with telehealth for DR management; first, with a remote patient evaluation, and then, second, referring the patient if symptoms are detected.

A Toronto-based, urban pilot screening program used a decision tree model to sort 566 patients into remote-manageable and in-person-visit-needed categories.[5] In this program, a patient identified as at-risk during a primary-care visit would be referred to the tele-retina program. The patient would then follow-up with a mobile ophthalmic clinic where a technician would dilate, image, take intraocular pressure and check visual acuity. The fundus image would be uploaded to a server, a retina specialist would evaluate the image, and the patient would be referred for an in-person, ophthalmic visit if positive for DR.

This triaging protocol helped prioritize specialists' time and sort DR patients efficiently. The study found that, versus a control group of in-person ophthalmic vis-

A patient self-images with the Home OCT (Notal Vision) home-based optical coherence tomography device.

its, tele-retina visits cost less ($109.29 vs. $315.22 Canadian per case diagnosed) and diagnosed more patients with DR (143 diagnosed in tele-retina visits vs. 79 diagnosed in standard-of-care in-person visits to initially identify DR).[5]

Arguably, the most exciting frontier in the evolution of teleophthalmology is the use of artificial intelligence in image analysis, the autonomous evaluation of fundus images for DR. Researchers imagine the final form of AI to be seamless imaging, analysis and generation of an ophthalmic referral if positive.

Improving AI evaluation incrementally

While we're not there yet, researchers are incrementally improving AI evaluation. In 2008, Michael Abramoff, MD, PhD, and colleagues built the first autonomous classifier: ARIAS (automated retinal image analysis system).[6]

In 2013, the refined model classified referable DR with a 96.8-percent sensitivity and a 59.4-percent specificity.[6] In the context of AI, sensitivity is the probability that given an image is positive for DR, the image will be marked as positive. Specificity is the probability that given an image is negative for DR, the image will be marked as negative. As of 2023, the ARIAS system, with further improvements, is used in the Scottish DR grading system as a first line of detection.[6]

Fundamentally, an AI-based identification of disease must perform similarly to clinicians in one or more areas. A 2023 Stanford study used the LumineticsCore reading system, formerly known as IDx-DR, one of the first Food and Drug Administration-approved autonomous, AI DR classifiers, and compared its interpretations with a team of physician readers on a macula-centered and an optic nerve-centered fundus photograph.[7]

In the detection of more-than-mild DR, researchers found LumineticsCore's sensitivity and specificity to be 95.5 and 60.3 percent, respectively. Remote specialists showed a sensitivity and specificity of 69.5 and 96.9 percent.[7] The study supported the use of AI in triaging DR and classifying patients for first detection. With DR prevalence predicted to increase by more than 50 percent globally in the next 30 years, AI could be the medical community's answer for quick and efficient triaging.[8]

The fundamental value add is that, via an autonomous AI modality, we can produce an earlier diagnosis of DR in patients who otherwise may not have access to timely evaluation. Ideally, AI identification would be available in community-based settings, such as pharmacies or grocery stores, or even passively via a mobile device (which we look at numerous times a day with both eyes), just like pedometers. Passive DR detection would then lead to a referral or a suggestion to see a retina specialist.

Ideally, AI identification would be available in community-based settings, such as pharmacies or grocery stores, or even passively via a mobile device. Passive DR detection would then lead to a referral or a suggestion to see a specialist.

Telemedicine in AMD management

AMD is amenable to observation and treatment when needed. Conversion to wet AMD is frequent enough that dry AMD patients should be monitored, and higher-risk patients or those with active exudation need to be properly identified to receive treatment in a timely manner.[9] Using AI and teleophthalmology, monitoring between in-person visits could be one way to better identify patients with recurrent exudation before symptomatic vision loss.

One recent remote monitoring study used the Notal Vision OCT device (*Figure, page 17*), a portable device that estimates the volume of fluid in the macula.[11] Forty wet AMD patients, each producing an average of six scans a week per eye, were both managed normally by an ophthalmologist and used the Notal OCT Analyzer (NOA) machine almost daily.

Of 35 in-office scans that came up as positive for fluid, the NOA found fluid in 31, an 89 percent accuracy rate. For 14 in-office scans that were negative for fluid, the NOA agreed on 10, a rate of 71 percent. The study authors described this as acceptable accuracy and sufficient for remote monitoring of stable patients who take frequent home scans.[10]

The economics of AI and telemedicine in retina

The dream is for someone to walk into a primary-care provider's office or grocery store, stop at a portable imager for a minute, and then receive a diagnosis and/or a referral to their closest ophthalmologist. This may even happen passively as part of a health app or feature on our mobile devices.

Artificial intelligence-enabled devices have good efficacy, but economic, regulatory and insurance hurdles remain. In 2018 the Food and Drug Administration approved IDx-DR, now LumineticsCore, the first device using AI to detect greater-than-mild diabetic retinopathy. Researchers propose that this device in a PCP's office would be transformative. Among people with diabetes who miss their annual eye exams, about 80 percent still see their primary-care doctor in the same year.[13]

At the same visit, with a LumineticsCore in-office, the patient could be remotely monitored for DR. Although the LumineticsCore sounds like a silver bullet, it is costly. A doctor could either buy the machine for around $13,000 (2021 price), lease it, or, for no charge by imaging a quarterly minimum of patients. Each examination cost the doctor a "click fee" or cost for each patient imaged regardless of reimbursement.

If AI-based imaging for diabetic retinopathy (CPT code 92229) were compensated on par with the remote imaging for retinal disease codes (CPT 92227 and 92228), doctors would lose about $4.69 per evaluation based on their average 2021 compensation.[14]

Limitations of AI software

While AI software is already available and approved for patient care and retina disease detection, each FDA-approved AI program is only reimbursable for use with certain fundus cameras. A primary-care clinic interested in using a new AI program would have to also invest significant capital to obtain the approved AI-based camera if they only own older, remote imaging telemedicine devices.

These barriers to AI use have led to frustratingly low adoption and utilization. Data gathered between 2021 and 2023 from the TriNetX database, a large dataset on health-care trends, showed that only 0.09 percent of people with diabetes even had a claim submitted for AI analysis of retinal imaging.[16]

The study authors tracked the trend with 92229 claim rates. In 2021, the data showed 29.3 claims per 100,000 patients; in 2022, this fell to 23.2 per 100,000, a significant 20.7-percent decrease.[15]

Challenges with reimbursement

Thus, one major hurdle for the proliferation of teleophthalmology is insurance compensation. During the early months of the COVID-19 pandemic, we saw a meaningful increase in the proportion of reimbursed remote imaging claims. In January 2020, 47.6 percent were paid. The proportion spiked to 56.7 percent in April and then returned to 45.9 percent by December. Evidently, the lockdown encouraged insurers to cover more remote cases.[16]

The trend shows that the progress made during the COVID-19 pandemic was quickly lost after the initial shock. Furthermore, a January 2020 study found that only 44.7 percent of teleophthalmology claims for remote DR screening were covered by non-capitated plans.[17]

It's important to note that regions with higher rates of DR often have worse retina imaging capabilities, limiting care for many.[18] From 2023 to 2024, compensation dropped for 92229, the code for autonomous retinal image analysis, from $46 to $40, discouraging the use of autonomous devices.[19]

Telemedicine and treat-and-extend

At-home testing seems particularly useful in treat-and-extend models where physicians dose patients on longer and longer intervals. Currently, ophthalmologists will extend patients by an extra one to two weeks. With at-home testing, patients could be managed with a more powerful data-driven approach based on the exact timing of detected exudation, ensuring a balance between adequate treatment and the burden of treatment.

With new, high-cost treatments such as aflibercept 8 mg (Eylea HD, Regeneron Pharmaceuticals) and faricimab (Vabysmo, Genentech/Roche) that promise extended dosing intervals, at-home testing could work as a safeguard during longer gaps between treatments.[11]

Many patients find it difficult financially and logistically to come in monthly. Longer treatment intervals with at-home testing would both provide insurance against silent, sudden bleeds and/or exudation when an interval proves too long, allowing patients to come in only when necessary. An OCT with at-home monitoring would be a significant improvement over the current treat-and-extend model.

AI and deep-learning models have also been proven to be accurate and applicable in AMD detection and prediction. One deep-learning model using OCT fovea images correlated a known incipient AMD biomarker with a new, unknown biomarker, highlighting the pre-wet AMD feature to researchers: hyporeflective outer retinal bands.[12]

Another particularly exciting model using a deep-learning algorithm predicted, with

(Continued on page 34)

Intraoperative FA: Putting it into practice

How to set up your surgical camera system for intraoperative fluorescein angiography and how it can help guide your surgical decision-making.


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By Lukan Mishev, MD, Nassim Abreu-Arbaje, MD, Joaquín Sosa-Lockward, MD, Lauren Gibson, MD, Aly Nguyen, MD, and Alan Franklin, MD

Take-home points

- For vitrectomy, intraoperative fluorescein angiography (IOFA) can accurately reproduce fluorescein biomarkers seen with FA in the clinic.
- The setup for IOFA is straightforward and reproducible. Once it's set up, switching to and from angiography mode during surgery is efficient and seamless.
- IOFA is a safe and efficient technique that can be done routinely and quickly after adding exciter filters into a light source and using digital barrier filters during digitally assisted vitreoretinal surgery.
- IOFA can effectively guide surgical decision-making.

Intraoperative fluorescein angiography can help to improve visualization of biomarkers during vitrectomy surgery, but its use seems to be more aspirational than practical. The advent of three-dimensional, high-definition surgical visualization promised to take IOFA during digitally assisted vitreoretinal surgery (DAVS) for pars plana vitrectomy for proliferative diabetic retinopathy and retinal vein occlusion in a new direction.[6,7] Here, we report on our modified approach that uses an optical exciter filter and either an optical or digital barrier filter to make it easier to switch to IOFA during vitrectomy surgery.[8]

Light sources and optical filters

The optical exciter filter can be placed in a number of different light sources, and a variety of filters are available.[9-11] To achieve the optimal fluorescein excitation, an optical filter with a dedicated wavelength of 475 to 490 nm should be inserted into the illumination light source. Different light sources have different spectrograms (*Figure 1*).

Based on the different emissions, we've found the Constellation Xenon (Alcon) illumination source has the best characteristic to detect fluorescein emissions. Spectrograms (*Figure 2*) demonstrate that Clarity 475 and Semrock 475 optical filters produce the best signal for fluorescein excitation. More recently, an LED light source from Geuder was shown to produce quality visualization as well.

Enhanced contrast is the key element of successful IOFA (*Figure 3, page 22*). To achieve this, we determine the optimal excitation source to maximum fluorescein signal intensity.

To create the optimal digital barrier filter recipe with an additional Notch laser 532 filter, a high dynamic range and sensitivity camera is essential to create an optimal digital barrier filter combination because the 532 laser filter can reduce the fluorescence intensity as it coincides with the wavelength emission of the fluorescein, 510 to 540 nm.

Based on our experience, we've found

that the Purepoint 532 (Alcon) laser filter may suppress fluorescence emission less than the Iridex 532 filter—based on spectrograms.[12] The Purepoint 532 filter also has swivel in-and-out design, so it can be removed during IOFA and not block any fluorescein emission. When we need to perform IOFA-guided endolaser, we engage the Purepoint filter and increase the gain on the camera to improve the image quality.

Digital barrier filters and signal

The digital barrier filter works by reducing the red and blue emissions to enhance the green signal. Then it alters the saturation and hue to diminish the blue-green color, enhancing the signal with brightness and contrast to produce a grayscale image similar to that from office-based fluorescein angiography (*Figure 4, page 22*).

The Ngenuity Version 1.5 platform (Alcon) can permit the operator to use computer modeling to optimize the signal once the operation is finished. Thus, the signal will be enhanced further secondary to the ongoing modifications of both the optical exciter and digital barrier output in this and other emerging DAVS platforms.

Both optical and digital barrier filters produce an excellent signal (*Figure 5, page 23*). So, if you don't have access to digital visualization, an optical barrier filter will work well with a standard optical microscope.

Machine and microscope setup

Although, the current IOFA protocol requires an initial setup, once the setup is complete, subsequent IOFA can be done rather seamlessly. Both the optical microscope and digital camera parameters must be optimized before adopting IOFA. This involves a simple task at the beginning of each day: properly cleaning and focusing the optical microscope and white light exposure or balance of the digital camera.

Once this is done, the switch to IOFA takes about 30 seconds and only involves switching the light to the source to where the optical exciter filters are located and changing the digital surgical channel or optical filter in the microscope. The switch back to standard visualization once IOFA is complete is equally efficient.[13] We've found that dual light output with a chandelier light source and a light pipe endoilluminator produces the best signal.

Surgical decision-making

In our experience IOFA provides additional feedback during vitrectomy surgery that can guide and

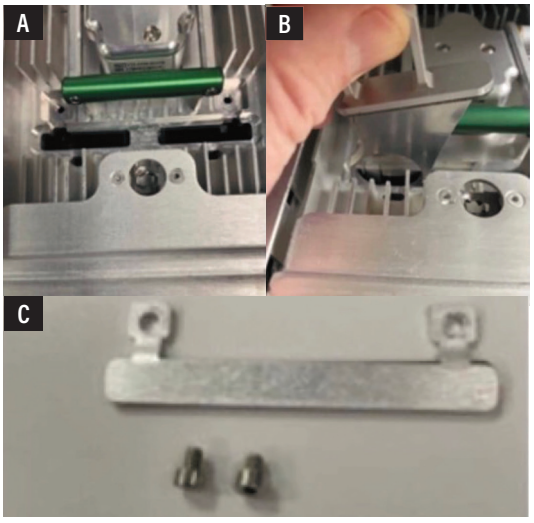

Figure 1. Preparation of the Constellation Vision System for intraoperative fluorescein angiography showing placement of the 485-nm bandpass filter exciter in the filter holder of the accessory light sources with steel modified washers. A) Access and location of the optical filter holders. B) Depiction of the removal of the filter holders. C) Filter holder screws and 4 mm hardware Allen wrench.

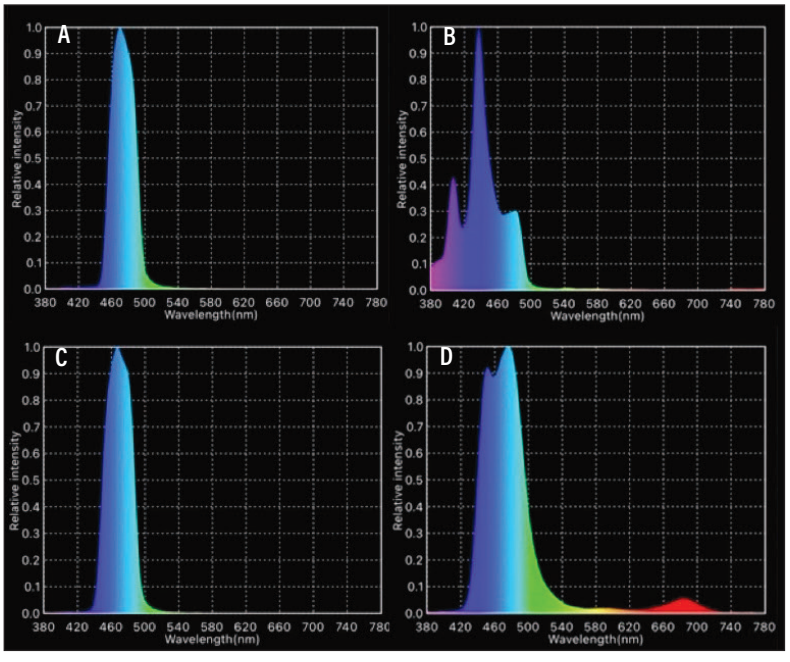

Figure 2. Spectrograms achieved by four different excitation filters ranging from 475 to 490 nm: A) Clarity 475; B) Omega 490; C) Semrock 475; and D) Leica 476. We chose to work with Clarity 475 and Semrock 475, due to their optimal peak wavelength and bandwidth. Omega 490 showed a spectrogram with peak on 440 nm and low emission in the desired 475-to-490 nm wavelength. Leica 476 emits more broadband in full color spectrum, which can potentially reduce the overall image contrast.

enhance decision-making.[14] For example, it can detect a delay in vascular filling time when a patient's blood pressure drops or intraocular pressure spikes, or if both happen.[13]

IOFA clearly visualizes vascular epiretinal membranes, maximizing the contrast between the vascularized fluorescent vessels against a dark background, which can be helpful to identify the correct surgical plane to delaminate. And it clearly visualizes both areas of residual abnormal vascularities and retinal ischemia when the delamination is completed.

To reduce the risk of postoperative vitreous hemorrhage while maximizing peripheral and night vision,[15] we treat these residual areas of abnormal vascular leakage with confluent laser, and place more confluent laser in the areas of peripheral ischemia while sparing the better perfused retina. IOFA can also be helpful in diagnosis and management, and ultimately guide surgical decision-making, when patients have media opacities, such as blood or inflammatory cells that occlude visualization of fluorescein biomarkers during the preoperative evaluation.

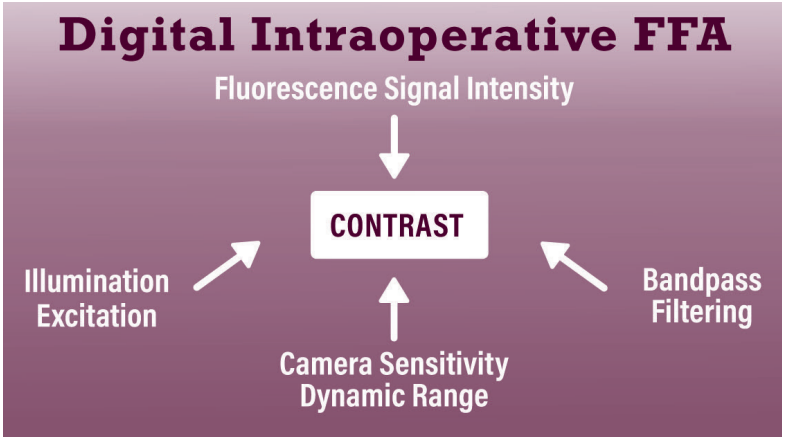

Figure 3. Schematic showing the components of intraoperative fluorescein angiography that modify contrast, which is critical for optimal visualization.

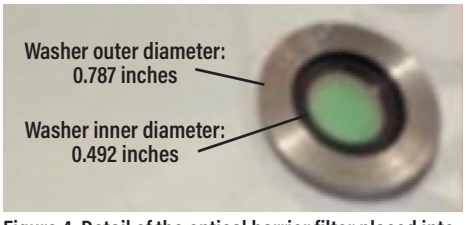

Figure 4. Detail of the optical barrier filter placed into the washer.

Safety and phototoxicity

The safety of FA has been well documented. The cutoff is 440 nm wavelength: toxicity could result below that. The bandpass exciter filters have a wavelength of 470 to 485 nm.[16,17]

However, the straight light pipe has been reported to cause light toxicity if it's held close to the retina for more than 15 minutes.[18] Because the fluorescein signal diminishes significantly after five to 10 minutes, the risk of significant phototoxicity is low.

Some authors have suggested that fluorescein may enhance laser burn intensity, but no reports exist of excessive laser burning with macular laser after FA in the clinic. Photocoagulation burns are rarely placed near the macular center.

In any event, we've found that a chandelier light source plus a light pipe endoilluminator held away from the retinal surface reduces the risk of any phototoxicity.[19] The International Commission on Non-Ionizing Radiation Protection (ICNIRP) published the "blue light hazard function," a wavelength-dependent weighting function, and guideline exposure limits.[20]

In more than 200 cases with IOFA, no light toxicity has been reported. However, it's important to proceed with clinical studies that confirm the lack of toxicity by measuring multiple different safety parameters postoperatively. They include vision, spectral-domain optical coherence tomography, multifunctional electroretinogram and visual fields to provide objective data on phototoxicity.

The future of IOFA

IOFA better delineates vascular preretinal membranes, and helps surgeons modify their intraoperative laser treatment.

Early data from 88 eyes that had IOFA-guided surgery demonstrate both improved vision and reduction in the rate of postoperative vitreous hemorrhage compared to

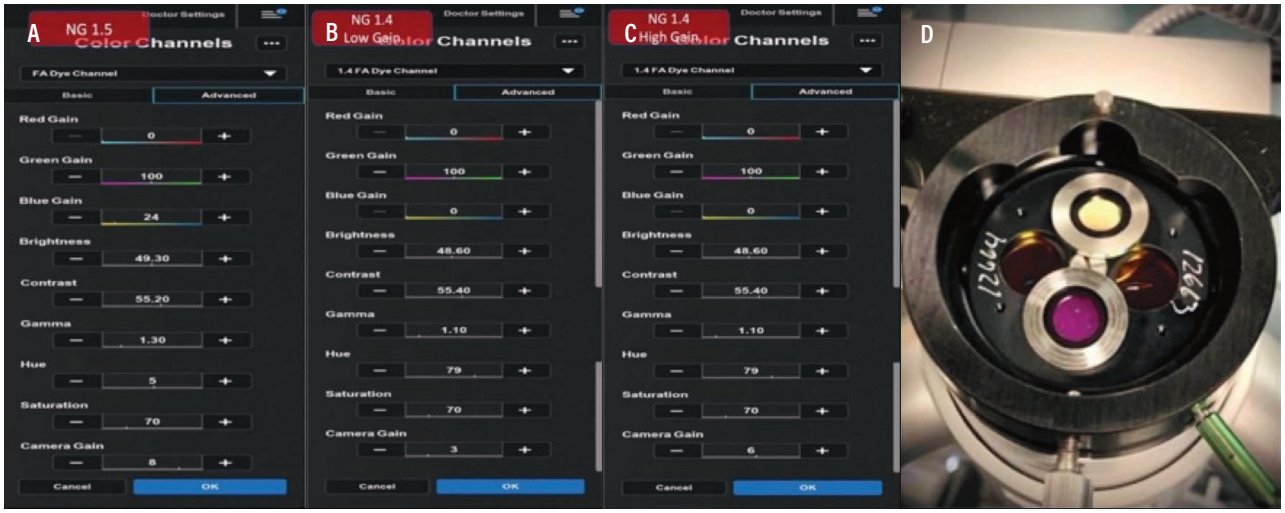

Figure 5. Optical barrier filter placement and digital barrier filter specifications. A, B, C) Specific color channels developed for intraoperative fluorescein angiography using Ngenuity for both software versions 1.4 and 1.5 showing the specifications of the digital filters or color channels. D) Placement of the optical filter and washer into the switchable laser filter.

standard vitrectomy: 10 to 12 percent vs. 30 to 40 percent. This helps to validate the potential benefits of adding IOFA to the surgical armamentarium during vitrectomy surgery.

Future efforts will aim to document safety measures, such as contrast sensitivity, multifocal ERG, microperimetry and visual fields in eyes that undergo IOFA. In addition, potential benefits may be associated with IOFA-guided laser for retinal vascular disease compared to standard panretinal laser.

Further, advances with optical exciter and digital barrier filters should lead to improved and more useful information. Thus, we believe that IOFA is an important developing technology to assist decision-making during vitrectomy surgery and ultimately will enhance patient outcomes.

***Acknowledgments**: The authors acknowledge the work of Jared Ridgeway, Miachanel Nguyen, Mariam Omar, Hudson Tate, Brenton Bickell and Ariel Shin for data entry and analysis.*

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Expert imaging recommendations for geographic atrophy

A look at the latest report from the Classification of Atrophy Meeting Group.

Nikhil Bommakanti, MD

Allen Chiang, MD

by Nikhil Bommakanti, MD and Allen Chiang, MD

Take-home points

- There are now multiple FDA approved therapies for GA.
- Advances in retinal imaging have revolutionized the ability to identify and monitor GA.
- Color fundus photography (CFP), fundus autofluorescence (FAF), near-infrared reflectance (NIR) and optical coherence tomography (OCT) can all be used to image GA.
- We recommend an OCT and NIR-based strategy with periodic FAF and baseline CFP.

Imaging is becoming an increasingly important aspect of managing age-related macular degeneration in general, and geographic atrophy in particular, with many studies prioritizing GA growth on imaging over visual function in terms of endpoints. Here, we'll review recent expert recommendations for the assessment of geographic atrophy using various imaging modalities

The GA Landscape

Geographic atrophy is a late form of age-related macular degeneration that's characterized by complete loss of the retinal pigment epithelium and outer retina of least 250 µm in diameter in the absence of macular neovascularization.[1,2] Dysregulation of the complement pathway is implicated in AMD,[3-5] and in 2023 the FDA approved two complement inhibitors, pegcetacoplan injection (Syfovre, Apellis Pharmaceuticals), which binds and inhibits centrally at the level of C3 and C3b and avancincaptad pegol (ACP, Izervay, Iveric Bio), which acts at C5, based on the results of the OAKS/DERBY[6] and GATHER1/GATHER2[7] clinical trials, respectively.

GA has historically been identified and monitored by funduscopic examination and color fundus photography.[8] Advances in retinal imaging, including fundus autofluorescence (FAF), near-infrared reflectance (NIR), spectral-domain optical coherence tomography (SD-OCT) imaging have revolutionized the ability to identify and monitor GA. In fact, as alluded to earlier, the primary endpoints of OAKS, DERBY, GATHER1, and GATHER2 relied on imaging, rather than visual acuity, endpoints.[6,7] GA imposes a significant burden on patients and, considering the recently FDA approved therapies, there's increased interest in the management of GA.

An international group of experts, the Classification of Atrophy Meeting (CAM) Group, has produced several important reports, including consensus guidelines for imaging protocols in AMD studies,[9] definitions of atrophy on OCT,[2,10] and descriptions of OCT features associated with progression to GA.[11] The group's recommendations are reviewed below, in

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the order that CAM addressed them in its report.

Color fundus photography

Color fundus photography (CFP) was used in the initial definition of GA and has historically been used to identify GA in clinical trials.[8] GA on CFP is defined as round or oval sharply demarcated areas with a hypopigmented or depigmented appearance and increased visibility of the underlying choroidal vessels *(Figure 1A)*. Advantages of CFP include the large volume of historical images for comparison and the true color rendition of the fundus (the white light captures images that look like just like how the macula appears on ophthalmoscopy).

There are several disadvantages, though. CFP images have low contrast, which can make it difficult to identify the border of a GA lesion. CFP also requires a bright light, which can make the result susceptible to image degradation from media opacities and is uncomfortable for patients. The CAM group recommends obtaining CFP at the baseline and final visits for clinical trials.[9] In practice, we often obtain CFP at baseline, but mainly rely on other modalities at subsequent visits.

Fundus autofluorescence

Fundus autofluorescence captures emission by intrinsic fluorophores, predominantly lipofuscin in the RPE,[12] and is a primary endpoint for clinical trials.[6,7,13] GA is hypoautofluorescent on FAF due to loss of the RPE, and FAF often provides a clear demarcation between atrophic and non-atrophic regions *(Figure 1B)*. Most devices use blue light for excitation, which can result in difficulty identifying GA that involves the fovea since the fovea in normal eyes is already hypoautofluorescent due to central macular pigments that absorb blue light *(Figure 2A)*.[9] Green light excitation FAF is available and can mitigate this problem, however supplementing FAF images with near-infrared reflectance images *(see below)* is also feasible and is more commonly done.

FAF uses a bright light that can be uncomfortable to patients and result in interference by media opacities, but in general it's well-tolerated, acquisition isn't difficult, and most OCT platforms and/or fundus cameras have the option of FAF capability. Given that it's a primary study endpoint used to delineate GA size and lesion characteristics, we periodically obtain FAF at least once or twice a year, particularly

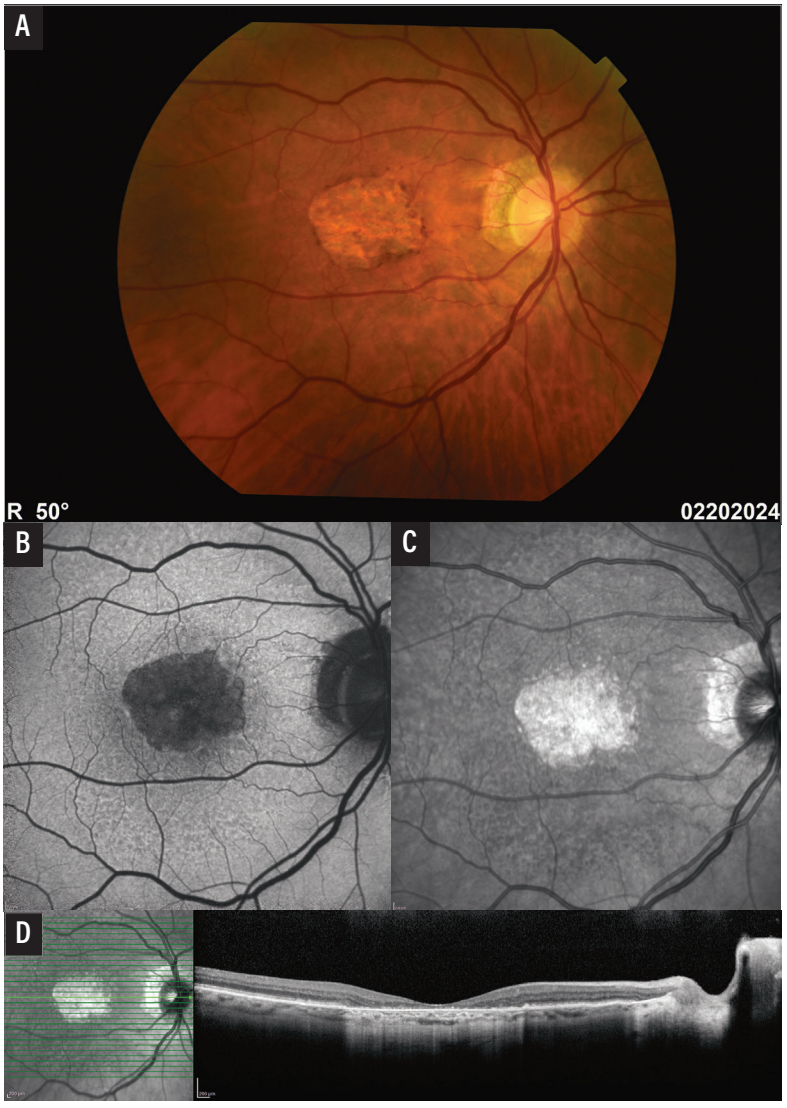

Figure 1. Multimodal imaging for geographic atrophy. Color fundus photography (A), fundus autofluorescence (B), near-infrared reflectance imaging (C), and optical coherence tomography (D)

in patients undergoing treatment for GA.

Near-infrared reflectance

Near-infrared reflectance imaging uses light at the higher end of the visible spectrum (750 to 840 nm). It initially started as a guidance modality for OCT, but it's now available as an independent output for many devices.[9] GA appears hyperreflective on NIR, and the borders are often also sharply demarcated, similar to FAF *(Figure 1C)*. There's no absorption by macular pigments (allowing easier visualization of GA involving the fovea; *Figure 2B*), lesions that predispose to GA (such as subretinal drusenoid deposits) can be seen well on NIR, and NIR is also comfortable for patients. Although use of NIR alone hasn't been well validated in studies, we find it to be very useful when obtained and interpreted in conjunction with OCT, particularly in cases where FAF image quality is suboptimal.

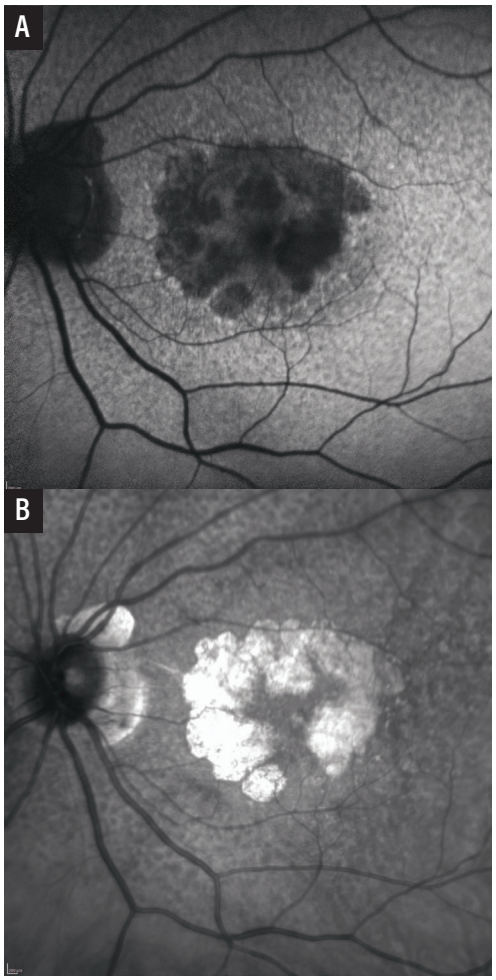

Figure 2. Near-infrared reflectance imaging as an adjunct to fundus autofluorescence. The fovea appears hypofluorescent on fundus autofluorescence as blue light is absorbed by macular pigments (A). Near-infrared reflectance imaging can be used to determine the presence or absence of fovea-involving geographic atrophy (B).

Multicolor imaging

Multicolor imaging combines blue (488 nm), green (518 nm) and near-infrared (820 nm) reflectance images obtained using confocal scanning lasers. Since different wavelengths highlight different details at different depths, this enables good images of the vitreoretinal interface and inner retina (blue), deeper retina (green), and outer retina and choroid (near-infrared) to be obtained. It's not yet clear, though, if this modality adds any utility beyond NIR so we don't routinely obtain multicolor images.

Optical coherence tomography

Spectral-domain and swept-source OCT provide high resolution, three-dimensional cross sections through the retina which provide information about the different retinal layers involved in GA. OCT B-scans can also be reconstructed into C-scans, which are *en face* images that can be selectively analyzed at varying depths within the retina, RPE and choroid.

Recognizing the utility of OCT imaging in this condition and the potential problems associated with the term "GA,"[1] the CAM group recommended OCT be used as the reference imaging modality to identify atrophy and proposed "complete RPE and outer retinal atrophy" (cRORA) as a broader term that includes GA as well as macular atrophy with coexisting or prior neovascularization.[2] cRORA is defined as 1) hypertransmission of at least 250 µm, 2) RPE attenuation of at least 250 µm, and 3) photoreceptor disruption (i.e., disruption of the IZ, EZ, or ELM, and/or thinning of the ONL) in the absence of an RPE tear, and is identified on OCT B-scans *(Figure 1D)*.[2] Although outside the scope of this article, OCT is also useful for identifying "incomplete RPE and outer retinal atrophy" (iRORA), which is nascent GA without MNV,[2,10] and lesions that predispose to GA.[11]

The near-infrared light used to acquire an OCT is comfortable for patients. Eye-tracking software and image registration, which improve colocalization analysis, enable the reliable comparison of scans over time. It takes longer to review OCT images because all B-scans of a volumetric scan or all en face slabs need to be reviewed, although AI-driven software will likely accelerate image processing in the future. OCT is essential in clinical practice, and we obtain OCT for all patients with GA at all visits. *(Continued on p. 33)*

Exploring the therapeutic possibilities of TNF inhibitors in retinal diseases

How TNF inhibitors may enhance retina treatment both alone and in combination with other drugs.

By Jyoti Sharma, PhD, and Eleftherios Paschalis Ilios, PhD

Jyoti Sharma, PhD

Eleftherios Paschalis Ilios, PhD

Take-home points

- TNF-α inhibitors open new therapeutic possibilities for treating retinal diseases, especially in controlling inflammation and preventing neuronal loss.
- Combining TNF-α and VEGF inhibitors enhances anti-angiogenicity and provides significant protection to the retina and optic nerve against neurodegeneration.
- Local administration of TNF-α inhibitors, by subconjunctival injection, improves drug bioavailability into the eye, while reducing the risks of systemic administration.
- Future therapies using bispecific antibodies, as well as non-viral gene therapies against TNF-α and VEGF may offer the opportunity to clinically employ the proposed therapy in the treatment of retinal disease.

Ocular diseases, such as uveitis, age-related macular degeneration, diabetic retinopathy and retinal vein occlusion, are leading causes of permanent vision loss worldwide,[1-3] and inflammation plays a critical role in the pathophysiology of these conditions, contributing to progressive retinal degeneration. Among the numerous cytokines implicated in ocular inflammation, tumor necrosis factor-alpha, a potent pro-inflammatory cytokine produced by reactive phagocytes and lymphoid cells, has emerged as a key player. This article explores the potential therapeutic role of TNF-α inhibitors in treating retinal diseases.

TNF-α involvement in retinal inflammation

TNF-α exerts its effects by binding to TNF receptors 1 (TNFR1) and 2 (TNFR2). TNFR1 is expressed ubiquitously across mammalian cells, while TNFR2 is primarily expressed in immune, endothelial and neuronal cells. In the retina, TNF-α is produced by a variety of cells, including microglia, infiltrating macrophages/monocytes, Müller cells and the retinal pigment epithelium. This cytokine contributes to tissue inflammation and damage by activating cell-death mechanisms. In tissues with non-proliferative cells, such as the central nervous system, this process leads to gradual neuronal cell loss and subsequent neurodegeneration. TNFR1 activation induces the expression of additional pro-inflammatory cytokines, chemokines and adhesion molecules, and increases vascular permeability, promoting the recruitment of reactive immune cells to the tissue.[4,5] Disruption of the blood-retinal barrier leads to neovascularization and further destabilizes retinal homeostasis. Inflammation also mediates ganglion cell loss, which precedes changes in pericytes or acellular capillaries, suggesting that inflammation and

Bios

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cell death independently causes vascular alterations.[6,7] Although VEGF inhibitors, currently used to treat retinal neovascular diseases, are effective against neovascularization, they have limited efficacy in suppressing pre-existing tissue inflammation. Consequently, combination therapies targeting both VEGF and TNF-α have been proposed and explored in relevant animal models.[8]

Therapeutic potentials of TNF-α inhibitors

Corticosteroids have long been the cornerstone of therapy for diabetic macular edema, retinal vein occlusion and AMD, effectively stabilizing vessel permeability and reducing exudative processes and macular edema. However, their broad action often leads to significant side effects due to a lack of specificity. This led to the development of monoclonal antibodies (mAbs), such as VEGF inhibitors, to specifically target retinal neovascularization.

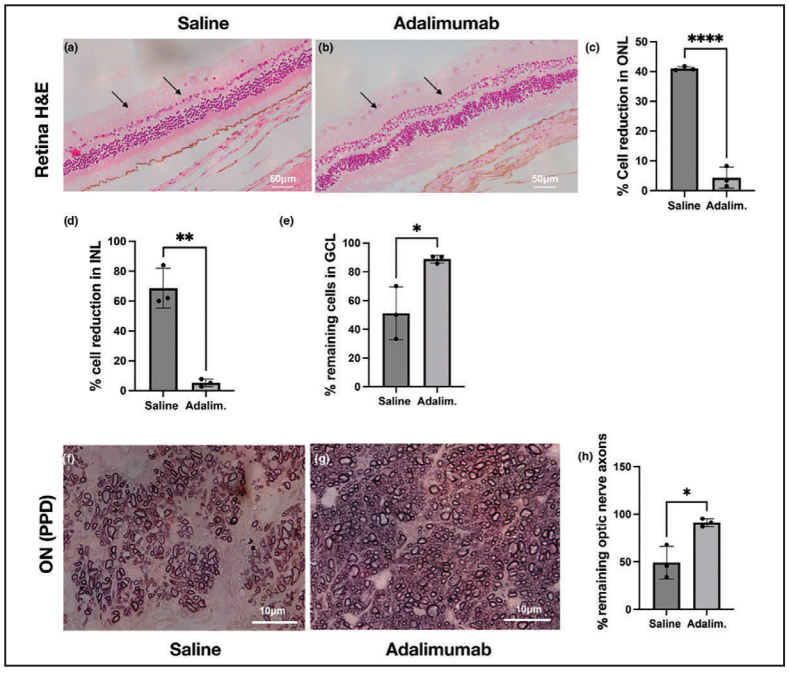

Figure 1. H&E and PPD staining three months after corneal alkali injury and subsequent treatment with a single subconjunctival injection of 4 mg adalimumab demonstrates significant protection to the retina and optic nerve.

Similarly, TNF-α inhibitors have become the gold standard for treating non-infectious uveitis, offering improved efficacy in suppressing inflammation compared to corticosteroids. Recent studies, including our own, have demonstrated that low-dose subconjunctival administration of adalimumab can prevent uveal and retinal inflammation, improving drug bioavailability to the retina by 10 to 100 times compared to systemic administration.[9,10] TNF-α inhibitors have also been shown to reduce ocular neovascularization in animal models, suggesting their potential use in treating neovascular diseases. In the context of alkali burns, TNF-α inhibitors were found to prevent secondary retinal ganglion cell loss and optic nerve degeneration (*Figure 1*), highlighting new prospects for their use in injuries. With the rapid expansion of biosimilars, TNF-α-targeting antibodies have the potential to revolutionize ocular disease therapy, particularly in terms of retinal protection.

Synergistic effect of combination therapy with TNF-α and VEGF Inhibitors

While TNF-α inhibitors can suppress ocular inflammation and neovascularization, some degree of angiogenesis may persist. VEGF inhibitors may be more effective against neovascularization, but they don't block inflammation, allowing neovascularization to potentially continue. We recently investigated the synergistic effects of concomitant TNF-α and VEGF inhibition, demonstrating that this combination enhances anti-angiogenesis and provides nearly complete blockade of vessel growth in an acute ocular injury model. Moreover, this therapy was able to prevent neuroretinal and optic nerve axon damage *(Figure 2)*, which is clinically very significant.

Current challenges

Although TNF-α inhibitors are effective against retinal inflammation and degeneration, they're associated with side effects

such as an increased risk of infections. Other complications include the development of anti-drug antibodies, malignancies, potential worsening of uveitis, and high costs. Physicians must weigh these risks against the potential benefits when considering TNF-α inhibitors as a treatment option.

Ongoing research suggests that many of these complications can be mitigated by local administration of the antibody, which may reduce the formation of anti-drug antibodies and lower the cost of the therapy. Additionally, combining TNF-α inhibitors with VEGF inhibitors could further enhance therapeutic potential, as preclinical studies have shown that anti-TNF-α/anti-VEGF therapy is more effective in preventing new vessel growth compared to VEGF inhibitors (aflibercept or bevacizumab), while also providing neuroretinal protection. Using a polymer-based drug delivery system, a single subconjunctival administration of anti-TNF-α (0.7 mg) and anti-VEGF (1.3 mg) offers long-lasting control of vascular growth for over three months.[10]

Bottom line

TNF-α inhibitors offer promising potential in treating retinal diseases, particularly in preventing retinal degeneration and enhancing the efficacy of VEGF inhibitors against neovascularization. These inhibitors significantly protect the retina and optic nerve from inflammatory damage. Future developments may include novel bispecific antibodies or small molecules targeting both signaling pathways, which could improve the clinical utility of this combination therapy. Additionally, incorporating innovative drug delivery systems could enhance therapeutic outcomes. Other prospects include the development of non-viral gene therapies targeting TNF-α and VEGF, with controllable gene expression for ophthalmic use. RS

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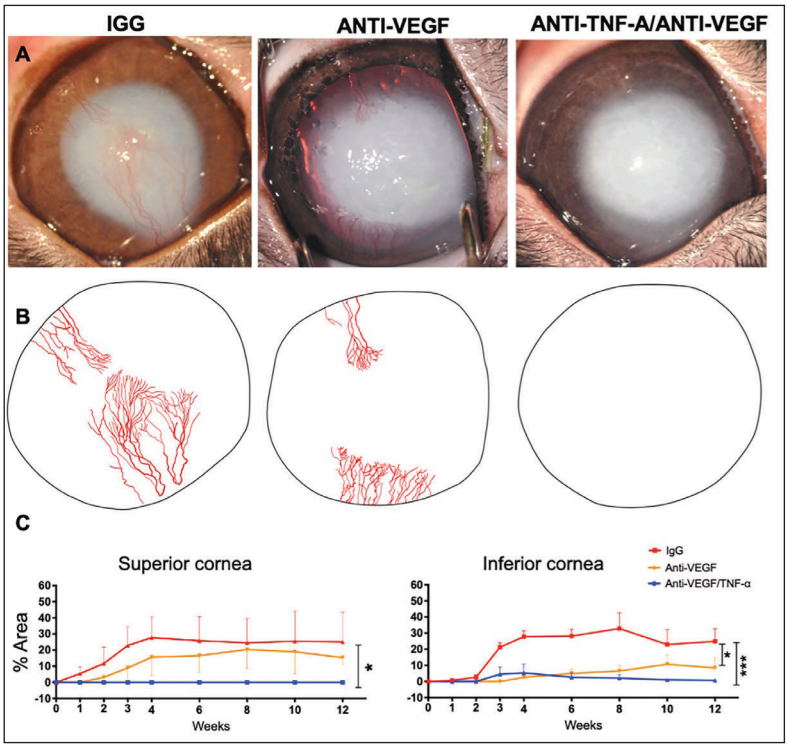

Figure 2. Therapeutic effect of single subconjunctival administration of anti-TNF-α/ anti-VEGF antibodies after severe ocular alkali injury.

Potential markers for AF, ROP and RRD

Studies on CRA message for CRAO, ranibizumab biosimilar switch and in-office pneumatic retinopexy also highlighted ASRS 2024.

Abstracts selected by Nikhil Bommakanti, MD
Reporting by staff

BIO

Dr. Bommakanti is a vitreoretinal surgery fellow at Wills Eye Hospital/Mid Atlantic Retina, Philadelphia.

DISCLOSURES: Dr. Bommakanti disclosed financial relationships with RegenXbio and Alimera Sciences.

The American Society of Retina Specialists crossed the pond to Stockholm for the 42nd iteration of its annual scientific meeting, which featured a multitude of trial readouts and reports on novel biomarkers and diagnostic techniques.

Retinal ischemic perivascular lesions a stroke biomarker in AF

Investigators at Yale School of Medicine in New Haven, Connecticut, set out to determine whether retinal ischemic perivascular lesions (RIPLs), an optical coherence tomography T biomarker of subclinical retinal ischemia, are associated with stroke in individuals with atrial fibrillation.[1]

Mathieu Bakhoum, MD, PhD, a retina specialist at Yale, and colleagues conducted a retrospective, cross-sectional study of 178 adults aged 50 to 90 years diagnosed with atrial fibrillation who had a macular OCT scan.

RIPLs were present in 41 percent of the patients and 16.9 percent had a stroke or transient ischemic attack. The researchers found no significant difference in anticoagulation use between patients who did and didn't have stroke or TIA.

A univariate analysis found that those with RIPLs had a three times greater risk of stroke (OR 3.01; 95% CI 1.33, 6.79, p=0.008). In a multivariable logistic regression model adjusting for age, sex, anticoagulation use, presence of hypertension, diabetes mellitus, vascular disease and congestive heart failure determined patients with RIPLs had a similar risk for stroke or TIA (OR 2.88; 95% CI 1.23, 6.98, p=0.016).

Using OCT to evaluate RIPL improves stroke risk stratification in patients with AF beyond the conventional clinical risk factors, Dr. Bakhoum said.

Dr. Bakhoum has no relevant financial disclosures.

OCT may identify potential ROP risk factor

Popcorn neovascularization occurs in higher-risk infants and may be an independent risk factor for retinopathy of prematurity progression. Isolated NV tufts are a common finding in patients with stage 2 and 3 ROP, noted J. Peter Campbell, MD, MPH, a pediatric retina specialist at Oregon Health and Science University (OHSU) Casey Eye Institute in Portland. He reported on a retrospective case series to more deeply explore classifying the course and significance of "popcorn" NV lesions in patients with ROP. [2]

The study used a prototype ultra-widefield optical coherence tomography device to captured *en face* scans (>140 degrees visual angle) from 136 babies in the neonatal intensive care unit at OHSU from December 2020 to August 2023. Their parents consented to participate in the study, but the study didn't account for demographic risk factors or other clinical confounders.

The investigators reviewed all images for the presence of popcorn NV along with standard zone, stage and plus classification. They used a cross-sectional analysis to compare eyes with and without popcorn by birth weight, gestational age and zone of ROP at the time of diagnosis.

Of the 64 patients with at least stage 2 ROP during their disease course, 22 (34 percent) developed popcorn NV. On average, patients with popcorn had lower birth weights (660.1g vs. 916.8g, p=0.001), lower gestational age (24.9 vs 26.1 weeks, p=0.01), and were more likely to present with zone 1 ROP (63.4 vs. 15.8 percent, p<0.001). They were also more likely to progress to stage 3 (68.2 vs 13.2 percent, p<0.001) and receive treatment (54.5 vs. 15.8 percent, p=0.002).

In the 13 babies who had images preceding onset of stage 3, popcorn developed

significantly earlier on average than stage 3 (35 vs. 37.5 weeks, p=0.04). Among eyes with stage 2 or 3 ROP at some point in their disease course, eyes with popcorn had a higher clinician-assigned peak vascular severity score than those without (5.9 vs. 4.2, p=0.006) On multivariable logistic regression, popcorn was independently associated with progression to stage 3, controlling for gestational age, birth weight and initial zone 1 disease.

Dr. Campbell noted that UWF-OCT was useful to visualize the progression of popcorn NV lesions and may help identify high-risk patients. Longitudinal monitoring of these lesions may be useful to better understand the pathophysiology of NV in ROP, he said.

Dr. Campbell is the owner of Siloam Vision.

Outer retinal corrugations may define regulated, dysregulated RRDs

Researchers in Toronto reported that swept-source OCT was able to detect significant morphologic differences between regulated and dysregulated rhegmatogenous retinal detachments.[3] Rajeev Muni, MD, MSC, of the University of Toronto and St. Michael's Hospital, reported that outer retinal corrugations (ORCs) are present in almost all dysregulated cases, but in only a few regulated cases.

The prospective cohort study included 122 eyes with RRDs, 21.3 percent (n=26) of which were classified as regulated and 78.7 percent (n=96) as dysregulated.

In patients with an identified causative break, horseshoe tears were absent in all regulated RRDs, but were observed in 87.3 percent of all dysregulated RRDs (p<0.001). Atrophic or small retinal holes were detected in all cases of regulated RRDs vs 12.5 percent of dysregulated ones (p<0.001).

OCT detected ORC in 3.8 percent of regulated vs. 84.4 of dysregulated RRD eyes (p<0.001). Cystoid macular edema was found in 50 percent of eyes with regulated RRD compared to 87.2 percent of eyes with dysregulated RRD (p<0.001).

Among patients with regulated RRDs, 31.3 percent were predominantly in Stage 2, none in Stage 3A, 6.3 percent in Stage 3B, none in Stage 4, and 62.5 percent in Stage 5.

In patients with dysregulated RRDs, 14.9 percent were in Stage 2, 16 percent in Stage 3A, 38.3 percent in Stage 3B, 23.4 percent in Stage 4, and 7.4 percent in Stage 5 (p<0.001).

The type of causative break, along with demographic and clinical features, differentiate regulated and dysregulated RRD, which may have implications for optimal management, Dr. Muni said.

Dr. Muni disclosed financial relationships with Bayer, AbbVie, Alcon, Apellis Pharmaceuticals, Precision Retina, Novartis, Bausch + Lomb, and Roche.

CRA message may restore perfusion on CRAO

Researchers in Mumbai conducted a retrospective analysis of 48 cases of central retina artery occlusion that didn't respond to conventional treatment to determine if central retinal artery massage (CRAM) would help in restoring perfusion by dislodging the causative thrombus.[4]

Nishikant Borse, MS, FMRF, of the Insight Eye Clinic, noted that a surgical intervention for CRAO has gained interest because conventional therapies have a limited role in CRAO management.

The surgical technique consisted of a three-port pars plana vitrectomy with 23- or 25-gauge needles, a low intraocular pressure vitrectomy, with infusion pressure at 8 to 10 mmHg and vacuum at 100 to 150 mmHg to prevent globe collapse. The low IOP during vitrectomy achieves an effect similar to paracentesis, Dr. Borse said. A prolonged and sustained hypotony that helps to improve perfusion is

The type of causative break, along with demographic and clinical features, differentiate regulated and dysregulated RRD, which may have implications for optimal management.

possible only by performing a vitrectomy, he said.

A complete posterior vitreous detachment is induced, a somewhat "tricky" maneuver during a low-IOP vitrectomy, Dr. Borse said. However, the PVD improved perfusion in the capillaries surrounding the disc. In all 48 cases, an absence of PVD was the single most common finding.

Following the vitrectomy, the peripapillary internal limiting membraned was stained using Brilliant Blue G dye. The ILM dissection was continued onto the optic disc. This was followed by a massage of the CRA and its branches radially from center to the periphery over the optic disc.

If the arterial sheath was thick, a careful sheathotomy was performed using end-gripping forceps. The sheathotomy was performed from the disc center at the origin of the CRA to the periphery in a radial fashion along the CRA branches.

If this maneuver succeeds, the retinal perfusion improves and the CRA can be seen pulsating at the level of the lamina, Dr. Borse noted. In many cases, further massage can result in the dislodgement of the causative embolus, which can be visualized migrating to the retinal peripheral circulation. Thus, low IOP during the procedure is imperative, he said. The eye has to be left hypotonic at the end of the surgery.

In the 48 patients Dr. Borse reported on, preoperative visual acuity in the affected eyes ranged from 20/400 to counting fingers. One month after surgery, visual acuity in 15 eyes (31 percent) had improved to >20/120; and in seven eyes (15 percent) to >20/200. Three eyes had a minimal VA visual improvement to 20/400. The remaining 23 eyes (48 percent) had no change in VA. VA rarely continued to improve beyond one month.

The results, Dr. Borse said, showed that mean logMAR visual acuity had improved from 1.61 at baseline 1.24 at one month. The difference between logMAR VA preoperatively and at one month postoperatively (−1.6 vs. −1.25, p=0.00000361) was statistically significant.

As for anatomical outcomes, retinal perfusion had significantly improved in 28 eyes by the end of the procedure. In nine eyes the causative embolus was successfully dislodged from the CRA to the retinal periphery. Preoperative fluorescein angiography showed that the arm-retina times were significantly below normal in all eyes with CRAO. FA three days after cannulation revealed complete reperfusion and incomplete but improved retinal reperfusion in 25 eyes.

Postoperative OCT demonstrated that the hyperreflective subretinal band had disappeared in eyes with successful reperfusion. However all the eyes showed some degree of retinal atrophy one month after even a successful surgery, due to the hypoxic insult, Dr. Borse said.

Dr. Borse disclosed financial relationships with Bayer India and Novartis India.

In a single-center study of more than 6,000 eyes, the biosimilar ranibizumab-eqrn was found to have similar safety and efficacy to reference ranibizumab in patients switched from the latter to the former.

Efficacy, safety equivocal post-ranibizumab biosimilar switch

In a single-center study of more than 6,000 eyes, the biosimilar ranibizumab-eqrn (RZE) (Cimerli, Sandoz) was found to have similar safety and efficacy to reference ranibizumab (Lucentis, Genentech Roche) in patients who were switched from the latter to the former. This is the first switching study of ranibizumab from clinical practice.[5]

The study by our group at Wills Eye Hospital involved a retrospective chart review of 6,717 eyes from 5,800 patients treated between November 2022 and December 2023 (RZE was approved in June 2023). Of those, 4,938 (73.5 percent) eyes had neovascular age-related macular degeneration, 1,193 (17.8 percent) had retinal vein occlusion and 586 (8.7 percent) had diabetic macular edema.

Eyes received 3.4 ±1.7 (total: 23,171) ranibizumab over 4.4 ±2.2 months. After switching, eyes received 2.5 ±1.2 (total: 16,688) RZE over 2.6 ±1.6 months (p<0.05). The ranibizumab group had no cases of endophthalmitis, the RZE group two (p>0.05).

Of the 2,444 eyes from 2,392 patients with at least three months of follow-up before and after the switch, change in central foveal

thickness was -87 ±4015 (median 0) for ranibizumab vs. -6 ±102 (median 0) for RZE (p>0.05). Change in visual acuity was 0.01 ±0.29 for ranibizumab vs. 0.00 ±0.25 for RZE (p>0.05). Subanalyses by indication yielded similar results.

Dr. Bommakanti has no relevant disclosures.

Largest study of in-office pneumatic retinopexy for RRD shows use and success rate rising

A database study that used the American Academy of Ophthalmology's Intelligent Research in Sight Registry may be the largest study to date evaluating the use of pneumatic retinopexy for in-office repair of rhegmatogenous retinal detachment.[6]

Gaurav Shah, MD, a retina specialist at West Coast Retina Medical Group, presented results of a nonrandomized retrospective cohort study of eyes with retinal detachment with retinal break. Dr. Shah noted that in-office PR is an alternative or adjunct to vitrectomy or scleral buckling, but PR may offer comparatively shorter recovery time, decreased cost, and lower risk of cataract progression.

The study evaluated 16,688 unique eyes that had PR for RRD from 2013 to 2022.

Nearly 90 percent of PRs were performed by retina specialists, and 43 percent of eyes were pseudophakic at baseline. The use of PR increased each year from 864 eyes in 2013 to 1,994 eyes in 2017, leveling off at about 2,000 a year from 2018 to 2021, and decreasing to 1,578 eyes in 2022.

The single-operation success rate was 59.5 percent, Dr. Shah reported. Median time to 20/40 best-corrected visual acuity or better was 231 days. Following PR, 1,741 eyes (10.4 percent) developed vitreous hemorrhage, 7,240 (43.4 percent) developed epiretinal membrane, and 54 (0.32 percent) developed endophthalmitis.

The Ophthalmic Mutual Insurance Co., through the Bruce Spivey Fund, provided funding for the study. Dr. Shah disclosed financial relationships with Zeiss and Regeneron. RS

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Application to clinical practice and bottom line

The approved therapies for GA are still relatively new, and there are many potential treatments in the research pipeline. Our understanding of GA continues to evolve, and our ability to detect it has improved thanks to advances in imaging.

FAF, NIR and OCT are all noninvasive imaging modalities that provide complementary information about GA. Clinical utility, acquisition time, patient comfort and cost all factor into the clinical decision to obtain any particular imaging test. We recommend an OCT-based strategy (we always obtain NIR with OCT) with periodic FAF when imaging GA. Although CFP has been used for clinical trials, we typically only obtain it at baseline. We don't obtain multicolor imaging.

Invasive and noninvasive angiography including FA, ICGA and OCTA are useful to either confirm or characterize macular neovascularization but are outside the scope of this article. Improved understanding of the histologic correlates to atrophic and pre-atrophic lesions on imaging as well as advances in technology, such as AI-driven image analysis, will inevitably enhance our ability to identify, monitor and possibly predict GA progression over time. RS

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acceptable error, the conversion of nonexudative AMD to exudative AMD in both the short (three months) and long term (21 months).[12]

Bottom line

David Glasser, MD, at the Wilmer Eye Institute at Johns Hopkins University in Baltimore, has made the point that the more equipment-heavy a subspeciality is, the less amenable its exam will be to remote treatment.[20] Unfortunately, this gap will only grow with the current trend of dwindling reimbursement.

The real tragedy, of course, is that the technology is already here, but the economics of reimbursement, regulatory hurdles, workflow and infrastructure hold back its utilization—real challenges standing in the way of AI and teleophthalmology to realize their full potential. If physicians and advocates can move the needle and strengthen teleophthalmology's current tools, countless patients will benefit. RS

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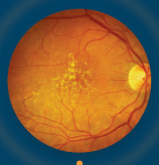

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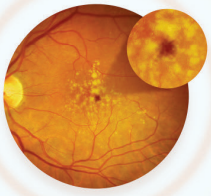

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