A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

VOL. 7, NO. 4 • JULY/AUGUST 2021

Retina Rounds: A tale of two hydroxychloroquine patients Page 13

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UPDATE ON DRUG DELIVERY

A closer look at EMERGING DRUG-DELIVERY platforms

An update on Port Delivery System with ranibizumab, a large-molecule anti-VEGF candidate and subretinal gene therapy to treat neovascular age-related macular degeneration. *Page 20*

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YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg:

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

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

(continued)

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

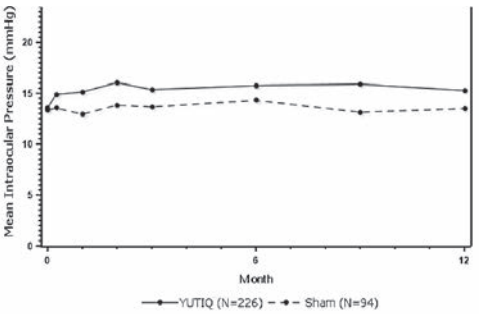
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

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

Table 2: Summary of Elevated IOP Related Adverse Reactions

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

Figure 1: Mean IOP During the Studies



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

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Fluid is bad. Or is it?

The story used to be so simple. Neovascular age-related macular degeneration is a leading cause of uncorrectable vision loss. In this context, intraretinal and subretinal fluid (SRF) is evidence of exudation from macular neovascularization (MNV). Treat every drop of fluid relentlessly with repeated injections. Unfortunately, this narrative is no longer so clear.

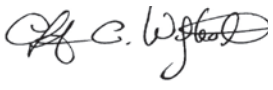
As we've observed, treated and studied countless eyes using optical coherence tomography and multimodal imaging, we've learned repeatedly that the truth is much more nuanced. In reality, not all fluid appears to be bad, and not all intraretinal and subretinal back-spaces are fluid that indicates an exudative process secondary to MNV. While these broad concepts are now well-appreciated and essentially obvious to most retina specialists, it's clear that we as a field still have much to learn about the meaning of all apparent fluid in AMD. Albert Einstein summarized the concept well: "The more I learn, the more I realize how much I don't know."

Take non-neovascular AMD. Defined by the absence of MNV, the simplistic view is that there should be no fluid present. Nevertheless, through a recent post hoc analysis of the Phase II FILLY trial studying pegcetacoplan (APL-2, Apellis) for the management of geographic atrophy, in which eyes developing investigator-determined exudative AMD were described, it was evident that a clinically relevant minority of patients had evidence of SRF or intraretinal cysts at baseline—fluid that was non-exudative in nature.

Such non-exudative intraretinal cystoid or cavitary spaces can occur within areas of retinal atrophy, potentially related to retinal pigment epithelium pump failure or Müller cell degeneration, the latter of which can be dramatic in some eyes with macular telangiectasia type 2. In comparison, non-exudative SRF can accumulate in eyes due to incomplete conformation of the outer retina to the underlying RPE, most commonly in the context of confluent drusen, in which fluid appears to accumulate in the valleys between drusen; or large drusenoid pigment epithelial detachments, in which fluid can accumulate at the apex of the lesion. The clinical implication of distinguishing such fluid from an MNV-driven exudative process is critical, and well summarized by Karen Jeng-Miller, MD, on page 30.

In exudative AMD, studies employing the Port Delivery System with ranibizumab (Genentech/Roche) implant, the anti-VEGF gene therapies ADVM-022 (Adverum Biotechnologies) and RGX-314 (RegenxBio), and next-generation anti-VEGF pharmaceuticals such as KSI-301 (Kodiak Sciences), CLS-AX (Clearside Biomedical) and EYP-1901 (EyePoint Pharmaceuticals), continue to shed light on the meaning of fluid and possibly more clinically impactful, fluid fluctuations.

While fluid in the context of AMD should raise a bright red flag indicating the possibility of associated MNV, beware that not all fluid is bad, and certainly not all fluid needs to be treated. RS



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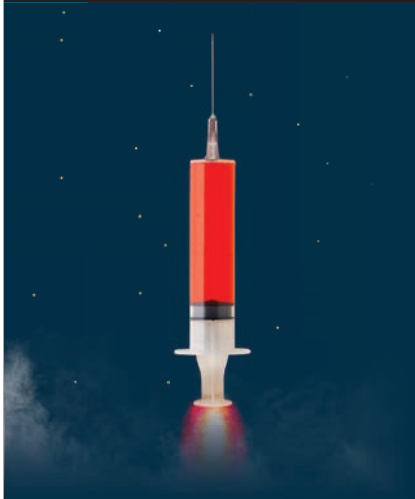

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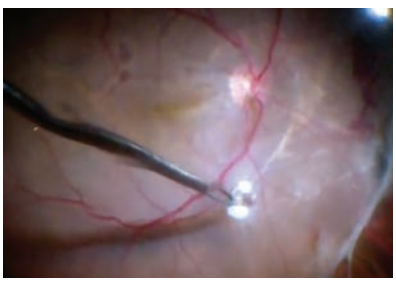

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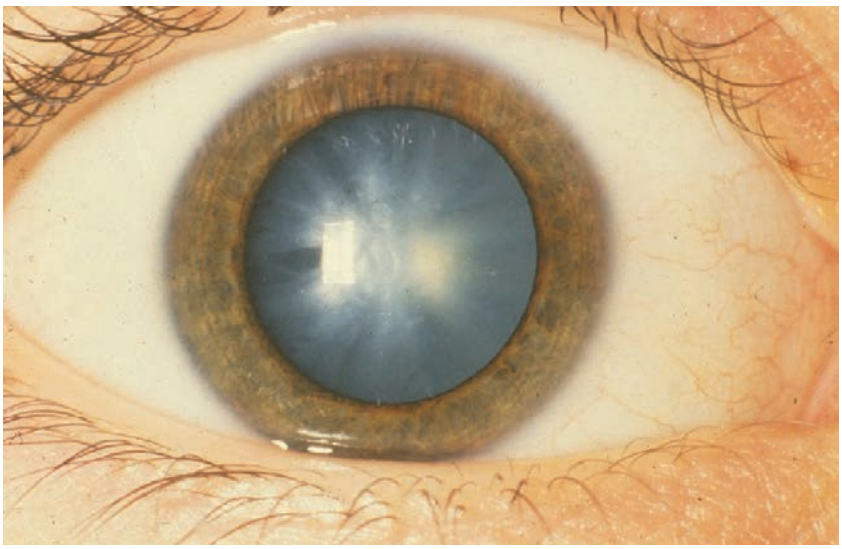
Finnish researchers add voice to cataract surgery in AMD debate

Retina specialists have long debated the timing for cataract surgery in patients with neovascular age-related macular degeneration. Now a team of researchers from Finland have weighed in with a small national study that adds more evidence in the "it doesn't matter" column.

"Our findings add data that cataract surgery should not be postponed due to fear of disease activation in wet AMD patients," Petteri Karesvuo, MD, of the University of Helsinki, tells *Retina Specialist*. "Central subfield macular thickness (CSMT) decreased postoperatively and increased only in one of 111 patients."

Dr. Karesvuo was the lead author of the study of patients with wet AMD who had cataract surgery at Helsinki University Hospital from 2014 to 2018.[1] "Injection intervals did not increase after cataract surgery," he adds.

"We found no justification to support delaying surgery until dry macula has been achieved," Dr. Karesvuo and colleagues wrote.



Finnish researchers say age-related macular degeneration shouldn't delay removing one of these.

CSMT, BCVA results

Their retrospective registry-based study evaluated best-corrected visual acuity and CSMT at three different intervals: at the time of nAMD diagnosis; the last time prior to cataract surgery; the first time after surgery; and at one year after surgery. They also documented the cumulative number of anti-VEGF injections at and after surgery, as well as systemic and topical medications.

"Cataract surgery did not significantly influence the incidence of hemorrhages, pigment epithelial detachment, intraretinal fluid or subretinal fluid when comparing macular status at surgery to that at first postoperative visit and at one

IN BRIEF

The Food and Drug Administration has accepted **Genentech/Roche's** Biologics License Application under priority review for the **Port Delivery System** with ranibizumab (PDS) for the treatment of neovascular age-related macular degeneration. The FDA is expected to make a decision on approval by October 23.

Novartis has terminated three studies investigating **Beovu** (brolucizumab) for the treatment of nAMD: MERLIN, RAPTOR and RAVEN. The decision came after Novartis reported the first interpretable year-1 results of the Phase III MERLIN study that showed a higher rate of intraocular inflammation, including retinal vasculitis and retinal vein occlusion, than aflibercept. Novartis says it will pursue an update to the Beovu prescribing information globally.

The FDA accepted the resubmitted New Drug Application from **Bausch + Lomb** and **Clearside Biomedical** for **Xipere**, the triamcinolone acetonide suprachoroidal injectable suspension. The FDA determined this is a Class 2 resubmission and assigned a Prescription Drug User Fee Act action date of October 30. The proposed indication is for macular edema associated with uveitis.

The FDA granted fast-track designation to **OPT-302, Opthea's** VEGF-C/-D "trap" inhibitor in combination with anti-VEGF-A therapy for neovascular AMD.

WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

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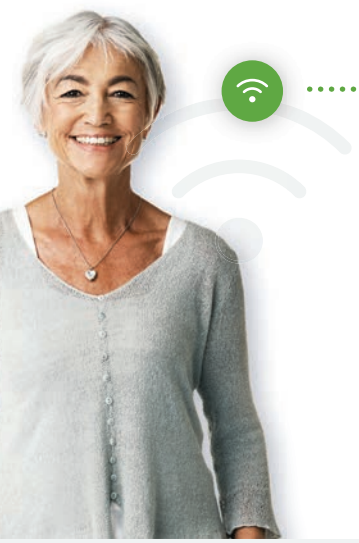

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References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina.* 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

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Quotable

"The CSMT change post-operatively or at one year did not correlate with patient age at surgery, nor with the preoperative BCVA"
— Dr. Karesvuo

year," the researchers wrote.

Among their key findings were:

- CSMT at the time of cataract surgery was 280.1 ±75 µm; CSMT postoperatively was 268.6 ±67.6 µm (p = 0.001); CSMT at one year was 265.9 ± 67.9 µm (p = 0.003).
- BCVA in logMAR units before surgery was 0.70 µm ±0.46 (Snellen equivalent median and intraquartile range [IQR]; 0.30, 0.125–0.40); postoperatively it was 0.39 ± 0.40 (Snellen equivalent median and IQR; 0.50, 0.32–0.80; p < 0.001); and at one year it was 0.33 ± 0.34 (Snellen equivalent median and IQR; 0.50, 0.32–0.80; p<0.001).
- The anti-VEGF treatment interval before surgery was 6.53 ±2.08 weeks; 7.03 ± 2.23 weeks at one year (p = 0.246); and 7.05 ±2.57 weeks at the last documented visit (p = 0.035).

Dr. Karesvuo and colleagues found that postoperative CSMT change inversely correlated with the preoperative CSMT levels (p < 0.001), but not with the cumulative number of anti-VEGF injections before surgery (p = 0.691). "The CSMT change postoperatively or at one year did not correlate with patient age at surgery, nor with the preoperative BCVA," they wrote.

The researchers repeated the multiple regression analysis to control for diabetes status and use of anti-inflammatory drugs, anticoagulants, calcium-channel blockers and statins.

The results remained consistent as only CSMT status before surgery was significantly correlated with postoperative CSMT change, while anti-VEGF treatment and presence of subretinal and intraretinal fluid were not.

More research needed

Dr. Karesvuo acknowledges that this isn't the final word on timing of cataract surgery in patients with wet AMD. "To get a better understanding of the cataract surgery in wet AMD patients, larger sample-sized studies would give more information," he says.

Additionally, future studies could evaluate the effect of cataract surgery in patients with newly diagnosed wet AMD, he notes. "In our study, the patients had a mean of 24.8 ±17.3 injections before surgery," Dr. Karesvuo says.

The researchers acknowledge that the small cohort size and short follow-up are limitations of their study, but note that one year of follow-up "is reasonably long enough to assess CSMT, visual acuity gain and anti-VEGF burden."

Dr. Karesvuo and colleagues have no relevant disclosures.

FOR THE RECORD

In the article "Will biosimilars find their place in retina?" in the May/June 2021 issue, ONS-5010/Lytenava (Outlook Therapeutics) was misidentified as a biosimilar of ranibizumab. It's a biosimilar of bevacizumab.

REFERENCE

1. Karesvuo P, Elbaz U, Achiron A, Hecht I, Kaarniranta K, Tuuminen R. Effect of cataract surgery on wet age-related macular degeneration activity. Acta Ophthalmol. Published online April 10, 2021. doi: 10.1111/aos.14864.

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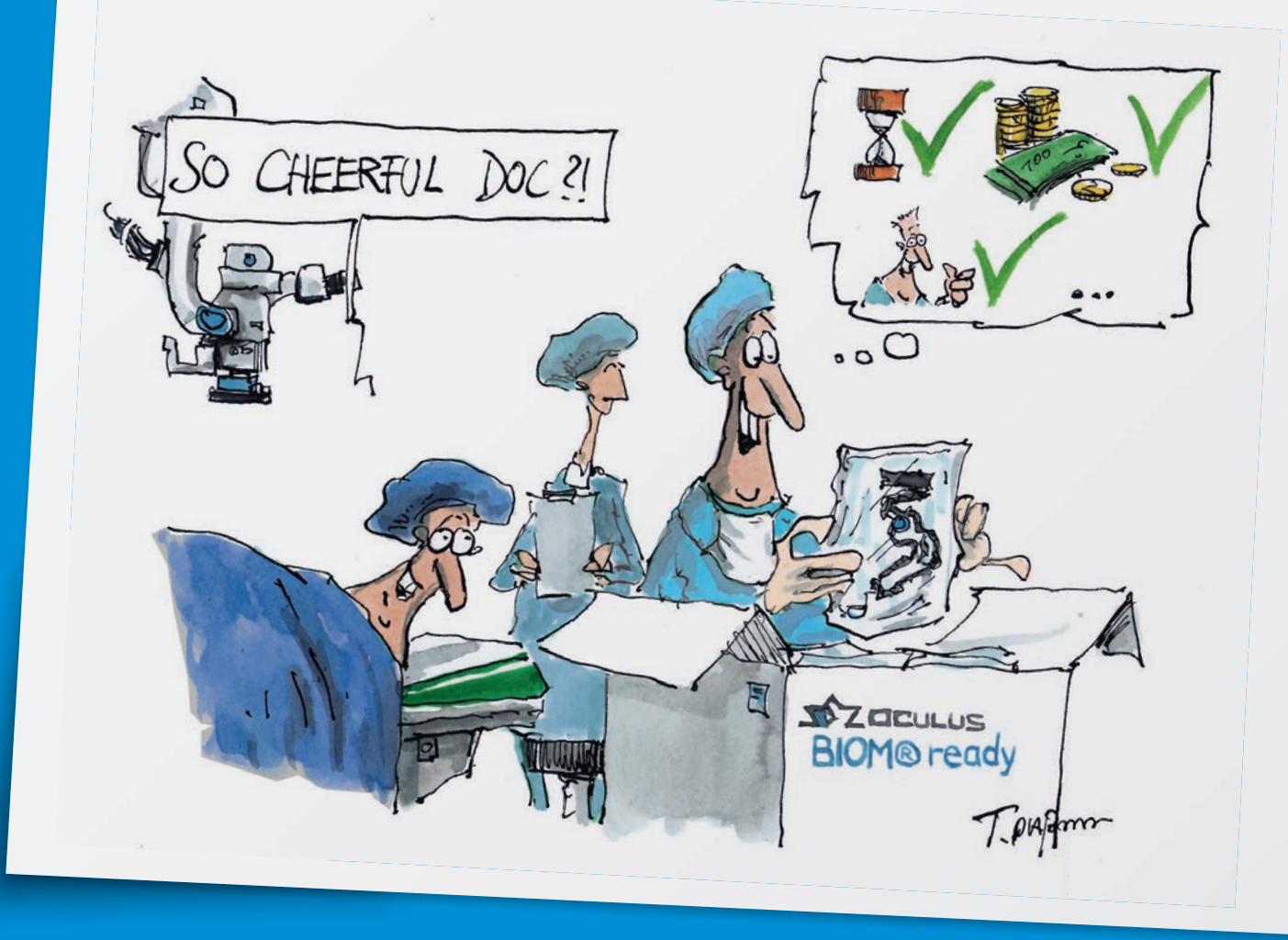

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Using a hAM plug for large macular holes

Human amniotic membrane can be a vision-saving option for macular holes larger than 800 µm.

By Tina Felfeli, MD, John Papanikolaou, and Efrem D. Mandelcorn, MD, FRCSC

Tina Felfeli, MD

John Papaniko-laou

Efrem D. Mandelcorn, MD, FRCSC

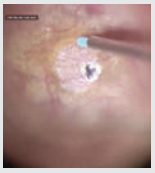
We previously described the macular hole hydrodissection technique for closure of large, persistent and recurrent macular holes.[1] This technique is effective in closing up to 87 percent of the most challenging macular holes, with 95 percent of patients experiencing vision improvement.[1] Despite the success of this technique, in our experience, for macular holes that are exceedingly large (>800 µm), a graft such as a human amniotic membrane (hAM) is often necessary to ensure complete closure.

Initial uses of hAM in ophthalmology

The amniotic membrane is the innermost layer of fetal membranes, with cells that possess a number of qualities suitable for use in regenerative medicine, such as low immunogenicity, promotion of epithelization and anti-inflammatory properties.[2] One of the earliest uses of hAM in ophthalmology was reported in 1940 by A. de Rötth, MD, for repair of conjunctival defects and reconstruction.[3] Subretinal implantation of the hAM was found to be tolerated in rabbits as Philip Rosenfeld, MD, and colleagues described in 1999.[4] RPE cells cultured on hAM have also been shown to maintain retinal homeostasis and improve eye function.[5]

View the Video

Watch as Drs. Felfeli and Mandelcorn demonstrate their technique for macular hole repair with a human amniotic membrane plug. Available at: https://bit.ly/RetSpecMag-202108



Use of hAM for macular holes

It's been suggested that hAM, in part because of its anti-inflammatory and pro-healing tendencies, serves as a highly effective biologic structural scaffold to promote centripetal migration of macular hole edges and resultant closure.[6] In 2018, a small case series of eight recurrent macular holes by Stanislao Rizzo, MD, and colleagues in Italy demonstrated a 100-percent closure rate with the use of hAM.[7,8] Studies have also shown partial recovery of macular sensitivity with microperimetric testing at the edges of the plug, with significant improvement in best-corrected visual acuity.[8]

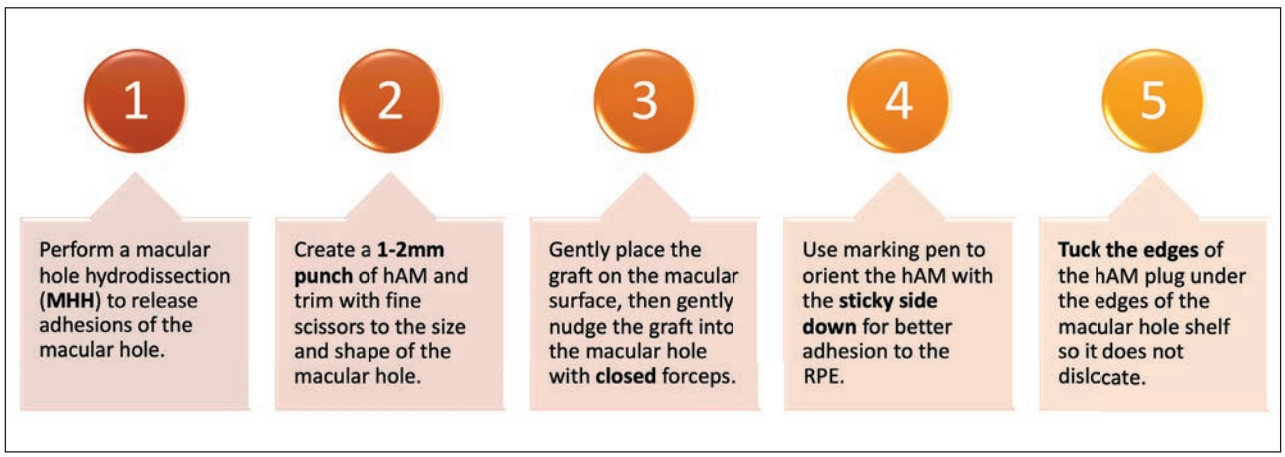


Figure 1. The five key steps in our approach to macular hole repair with human amniotic membrane.

Our approach to MH repair with hAM

There are a few critical steps in hAM macular hole surgery that are important to consider when placing a hAM in a macular hole (*Figure 1*). First, one of the most important steps is to ensure that any adhesions of the macular hole to the underlying RPE are well-separated. This can be achieved with the macular hole hydrodissection (MHH) technique by manipulating the edges of the macular hole with a soft-tipped cannula with proportional reflux, followed by gentle passive aspiration.[1] This process creates a shelf between the macular hole edges and the retinal pigment epithelium, under which the hAM can be placed.

Next, we use a 1-to-2-mm punch to fashion the amniotic membrane graft. We often trim this with fine scissors to a size just a little larger than the macular hole so the graft will fit nicely in the macular hole. It's important that the diameter of the plug almost matches the macular hole, because plugs smaller than the macular hole won't attach under the shelf of the macular hole edges, and larger plugs won't fit in the macular hole or create folds from tissue redundancy.

We then place the hAM in the vitreous cavity with a fine gripping forceps and tuck it into the space created around the macular hole edges. It's helpful to gently place the graft on the macular surface so it doesn't float away, and then nudge

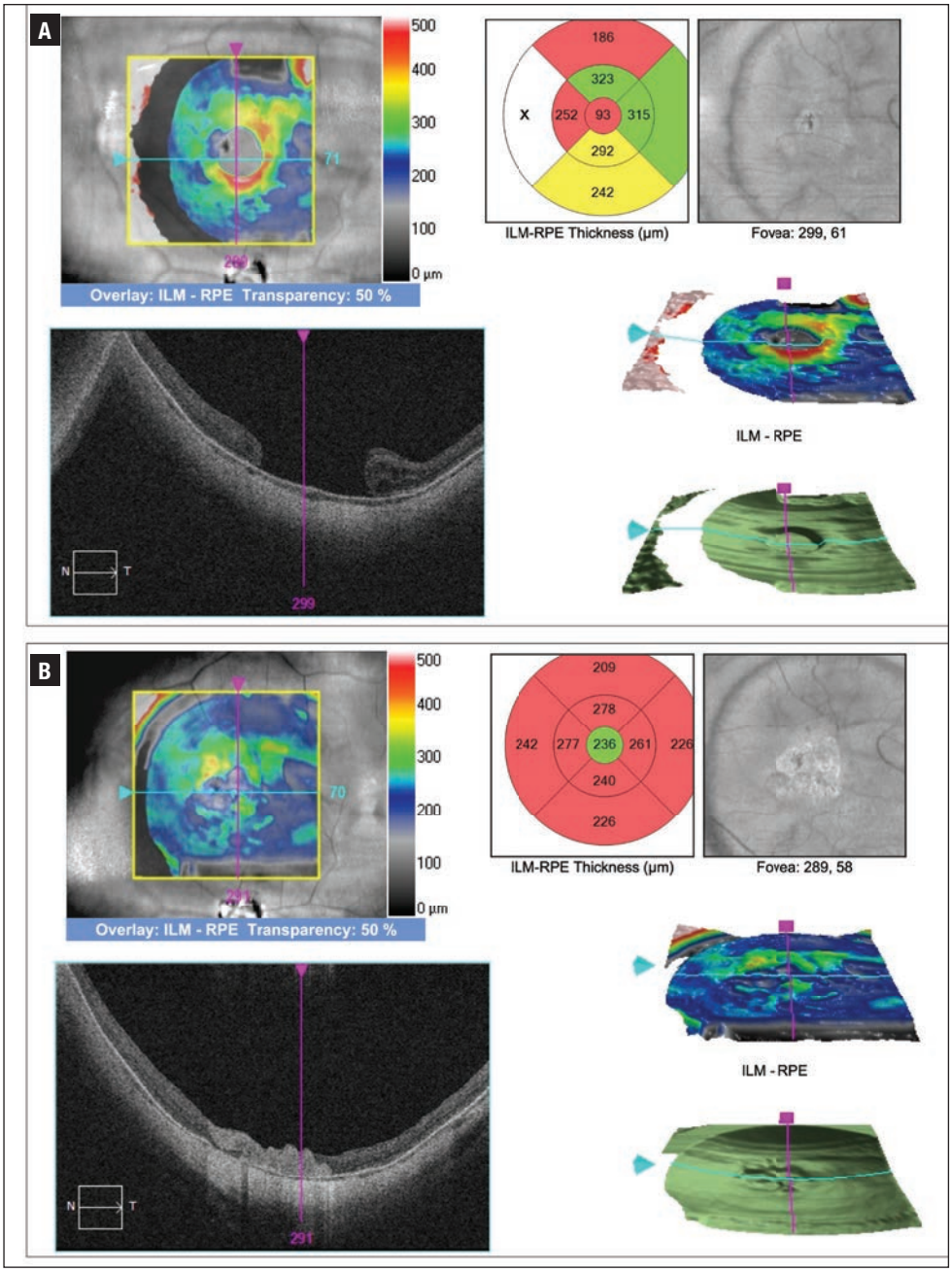


Figure 2. Optical coherence tomography macular cube scans before (A) and after (B) macular hole repair with the macular hole hydrodissection technique and human amniotic membrane.

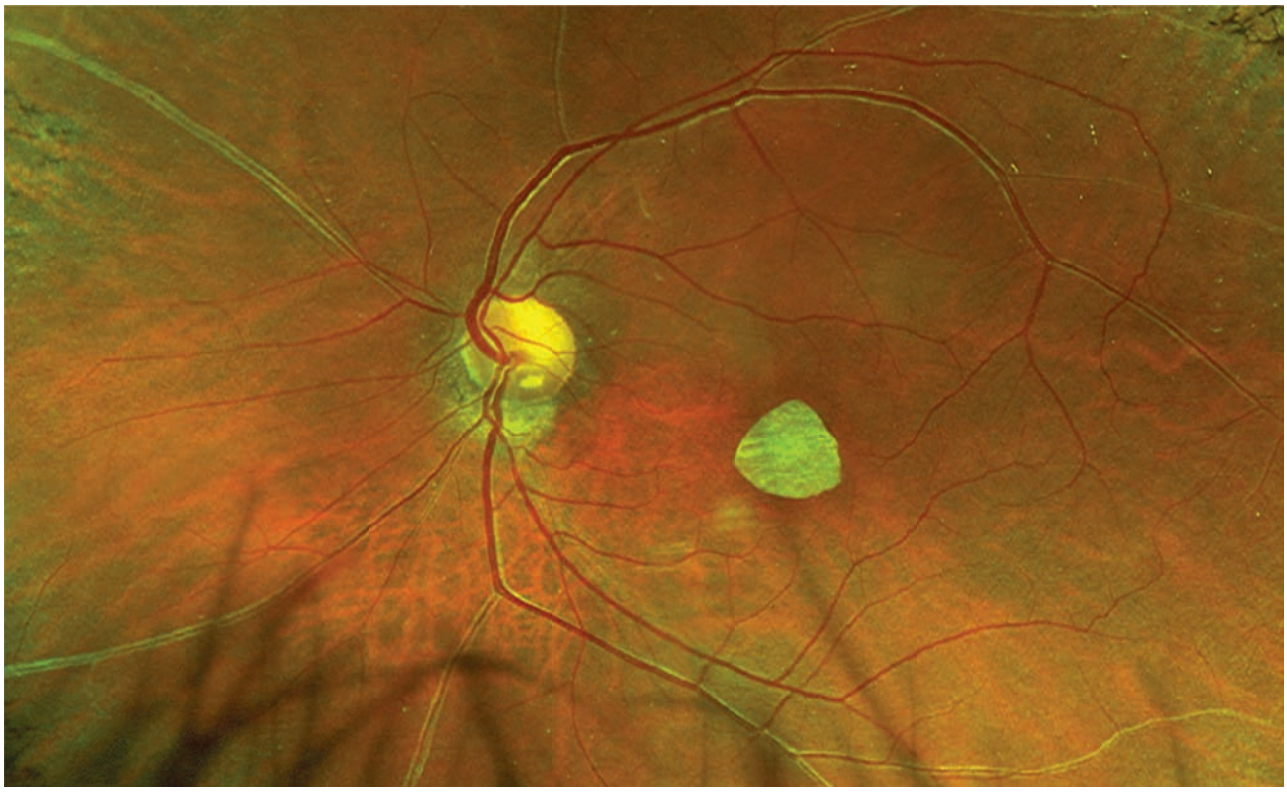


Figure 3. Widefield color fundus photography depicts a well-positioned round-shaped human amniotic membrane plug in the macular area following macular hole repair.

Bios

Dr. Felfeli is an ophthalmology resident at the University of Toronto.

Mr. Papanikolaou is a research student at University Health Network, Toronto.

Dr. Mandelcorn is an associate professor of ophthalmology at the University of Toronto.

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

the graft into the hole with the closed forceps so it doesn't stick to the teeth of the forceps.

It's also important to place the graft with the stromal layer side down (it's sticky and non-shiny) so it will adhere to the RPE once it's in the macular hole. We often mark the non-sticky side with a small dot using a marking pen so we can identify it once it's placed in the vitreous cavity. The plug edges are tucked under the edges of the macular hole shelf. This is a crucial step to ensure the hAM graft doesn't dislocate postoperatively. A fluid-air exchange is carried out and the eye is then flushed with SF6 gas (20%).

A case of MH repair with hAM

The accompanying video shows a case of a 52-year-old woman with a history of high myopia and surgical repair for a macular hole-related macular detachment with a persistent open MH. She had been followed for four years and decided to undergo secondary repair of her macular hole that was measured preoperatively at 1,458 µm with a visual acuity of 20/400 (*Figure 2, page 11*). She underwent MHH with a hAM plug and had an excellent anatomical closure of the macular hole. Her postoperative visual acuity recovered to 20/70 at seven months.

Figure 3 depicts another case with a well-positioned round-shaped hAM plug as shown on a color fundus image.

Alternative techniques

Alternative techniques using lens capsular flap, autologous transplantation of the internal limiting membrane and neurosensory retinal free flap, and autologous

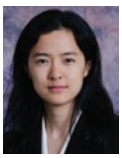
(Continued on page 18)

A tale of two hydroxychloroquine patients

Two cases demonstrate the spectrum of retinal findings in HCQ retinal toxicity as well as the role of multifocal electroretinogram in detecting the condition.

By Alexandra van Brummen, MD, Amy Yuan, MD, and Lisa Olmos de Koo, MD, MBA

Alexandra van Brummen, MD



Amy Yuan, MD

Lisa C. Olmos de Koo, MD, MBA

A 74-year-old Caucasian woman came to the retina clinic as a referral for evaluation of possible hydroxychloroquine toxicity. Her chief complaint was blurry vision in her right eye. She had a history of hydroxychloroquine use for 27 years for Still's disease, at a current dose of 200 mg every other day.

History of HCQ use

While she never exceeded an HCQ dose of 5 mg/kg/day, she did have a period of simultaneous tamoxifen use while she was undergoing treatment for breast cancer. Her Still's disease was refractory to multiple other immunomodulatory agents.

Her ocular history was significant only for recent cataract surgery in the right eye, and she was being monitored as a glaucoma suspect. On examination, her best-corrected visual acuity was 20/25 OD and 20/20 OS. Intraocular pressures were normal. Pupillary reactions were normal without an afferent pupillary defect, and extraocular movements were full. The slit lamp and dilated fundus examinations didn't have any significant findings.

Optical coherence tomography (*Figure 1*) demonstrated outer retinal loss on either side of the fovea, which was more prominent in the left than the right eye. Given these findings, a multifocal electroretinogram (mfERG) was obtained to evaluate for evidence of photoreceptor dysfunction. The first mfERG was found to have modestly decreased amplitudes, equivocally within the limits of normal, but possibly representing early toxicity (*Figure 2A*). A repeat mfERG one year later demonstrated more definitive evidence of amplitude reduction, consistent with drug-induced retinal toxicity.

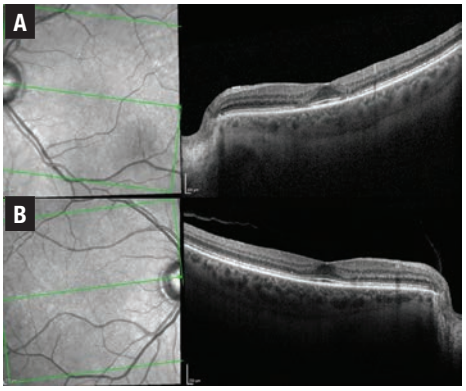


Figure 1. Optical coherence tomography of the left (A) and right (B) eyes demonstrate left outer retinal loss in the inner segment/outer segment junction more so than in the right.

A second case of HCQ toxicity

A 58-year-old woman of Asian descent was referred to the retina service for blurring in her left eye. She denied any focal scotomas or metamorphopsia. She had an ocular history of dry eye and used Restasis (cyclosporine 0.05%, Allergan/AbbVie).

Her medical history included Sjögren's syndrome, lymphoma and cryoglobulin-

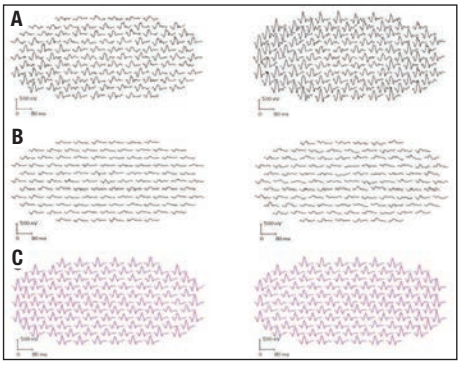


Figure 2. Multifocal electroretinogram (mfERG) of patient one (A) and patient two (B) both show reduced amplitudes suggestive of decreased retinal function, more pronounced in patient two. C shows a normal mfERG for comparison.

UW Medicine EYE INSTITUTE

Dr. Olmos de Koo is an associate professor of ophthalmology and chief of the retina service at the University of Washington in Seattle, where Dr. van Brummen is an ophthalmology resident and Dr. Yuan is a retina fellow.

emia. She had been taking HCQ 200 mg daily, with a short period of 400 mg daily, for 10 years. She denied any allergies to medications.

Visual acuity was 20/20 in both eyes, with normal intraocular pressures. Pupillary reactions were normal without afferent pupillary defect, and extraocular movements were full. Slit lamp and dilated fundus exams were notable only for a peripheral choroidal nevus in the left eye.

We ordered fundus autofluorescence to evaluate for possible HCQ toxicity. It demonstrated hyperautofluorescence following the arcades in the left greater than the right eye (*Figure 3*). OCT demonstrated focal peripheral areas of the inner segment/outer segment (IS/OS) junction loss in a pattern corresponding to the areas of hyperautofluorescence.

Given these findings, we obtained a mfERG, which demonstrated diffuse slowing and amplitude reductions (*Figure 2B*) and highlighted dysfunction that wasn't detected on screening Humphrey visual field (HVF) testing (*Figure 4*).

Diagnosis and management

Given the multimodal imaging findings, both patients were counseled about the risk of progressive retinal toxicity and irreversible vision loss with ongoing hydroxychloroquine use. After discussing alternative methods of managing their respective systemic diseases with their rheumatologists, both patients ultimately decided to discontinue their HCQ. Both have had stable ocular findings on OCT and fundus exam without evidence of worsening toxicity since.

These cases demonstrate the utility of mfERG in the diagnosis and management of HCQ toxicity. In both patients, mfERG helped demonstrate functional retinal damage at the outset, which served as a helpful tool to both provide objective data in the diagnosis of HCQ toxicity, as well as in counseling them to cease using the medication. Of note, minimal changes were seen on prior screening HVF testing for the second patient leading up to her referral to our clinic, in contrast to the changes seen on mfERG.

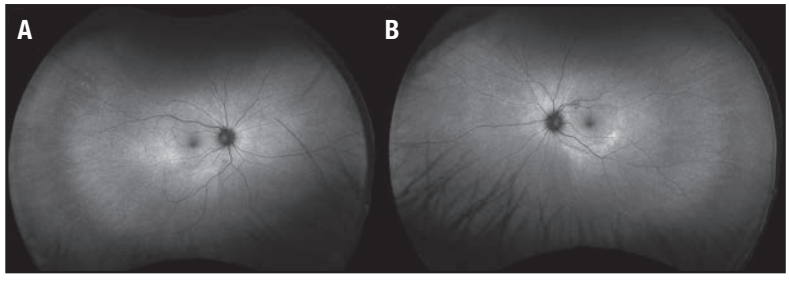


Figure 3. Fundus autofluorescence of the right (A) eye shows hyperautoflourescence in the peripheral macula and around the nerve, and superotemporal hyper- and hypoautoflourescence focally corresponding with a nevus. The left eye (B) shows hyperautoflourescence in the inferior peripheral macula and around the nerve, with speckled hypoautoflourescence in the superonasal macula.

How to screen for HCQ toxicity

HCQ toxicity can be subtle and usually develops after years of treatment. The risk is low, with incidence previously described at 0.5 to 2 percent of patients with extended use.[1-4] However, these estimates are thought likely to underestimate the extent of toxicity.[1]

Risk of toxicity has been found to be dose dependent. Patients on doses <5 mg/kg (actual body weight) have a less than 1 percent risk in the first five years and a less than 2 percent risk in 10 years of treatment.[5]

Increased risk has been noted in >1,000 g cumulative dose, >5 mg/kg/day treatment, more than five years of use, kidney disease, tamoxifen use, as well as history of macular degeneration and other retinal diseases.[1,5] Tamoxifen use is especially important to elucidate, given it has been shown to cause a fivefold increased risk in toxicity.[1,5] In addition, older age, liver disease and some genetic variants in *ABCA4* have been found to increase the risk as well.[5]

The American Academy of Ophthalmology published updated recommendations for HCQ toxicity screening in

2016, recommending a baseline fundus examination in the first year of use to detect any preexisting retinal abnormalities, then yearly afterward in the absence of any of the previously mentioned risk factors.[5]

Recommendations for HCQ toxicity

The AAO recommendations recognized that most providers will use spectral-domain OCT and HVF in conjunction with the fundus exam to screen for subtle changes related to HCQ toxicity, but noted this isn't required at the baseline examination unless abnormalities are apparent on examination. The recommendations encourage use of SD-OCT and HVF at follow-up to help detect toxicity, and strongly recommend these more objective tests if a diagnosis of toxicity is made.[5]

Ronald B. Melles, MD, and colleagues further described in their study that 50 percent of patients of Asian descent had pericentral changes (more than 8 degrees from the fovea), compared to 2 percent in white patients[6]—an observation that correlates with the findings in our second patient.[6]

Screening recommendations for patients of Asian descent call for 24-2 HVF rather than the 10-2 HVF screening to better determine peripheral changes. However, on both 10-2 and 24-2 HVF nonspecific changes can be difficult to interpret, and the subjective nature of the study limits their use as a screening tool.

Fundus autofluorescence has also been suggested as a useful tool to augment sensitivity in testing, and can demonstrate early changes prior to retinal pigment epithelium changes from toxicity.[5,7,8]

More recently, mfERG has been suggested as an adjuvant tool in suspicious cases to demonstrate functional changes,[8] as the findings may be more objective and subject to less variation and confounding factors than HVF testing. Indeed, the cases we present here illustrate the utility of mfERG in management of HCQ toxicity.

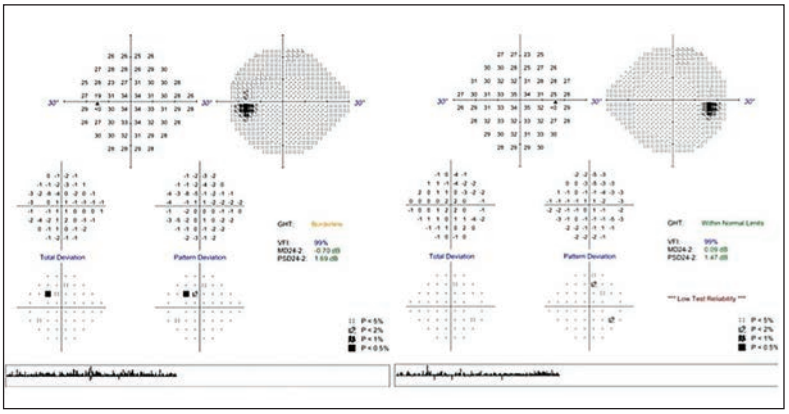


Figure 4. On initial screening, Humphrey visual fields of patient two demonstrate minimal changes.

Bottom line

HCQ toxicity is rare, but it can be severe and it is irreversible. The risk of toxicity increases with greater duration of use, higher doses and with retinal disease and systemic toxicity. SD-OCT, FA and HVF augment the sensitivity of the physical exam to pick up on early changes in hydroxychloroquine toxicity. Multifocal electroretinogram may help to correlate functional photoreceptor loss to anatomical changes to better diagnose toxicity and justify stopping HCQ for patients.

More recently, mfERG has been suggested as an adjuvant tool in suspicious cases to demonstrate functional changes, as the findings may be more objective and less variable and confounding than HVF testing.

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Removing thick subretinal PVR bands

Subretinal proliferation is a well-known component of proliferative vitreoretinopathy. Here's how to deal with it.

By Rahul Reddy, MD, MHS, and Setu Patel, MD

Rahul Reddy, MD, MHS

Setu Patel, MD

Bios

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Dr. Hahn is a partner at New Jersey Retina in Teaneck.

DISCLOSURES: Dr. Reddy is a consultant to Allergan/AbbVie, Regeneron Pharmaceuticals, Alimera Sciences, Bausch + Lomb and EyePoint Pharmaceuticals.

Dr. Patel has no relevant relationships to disclose.

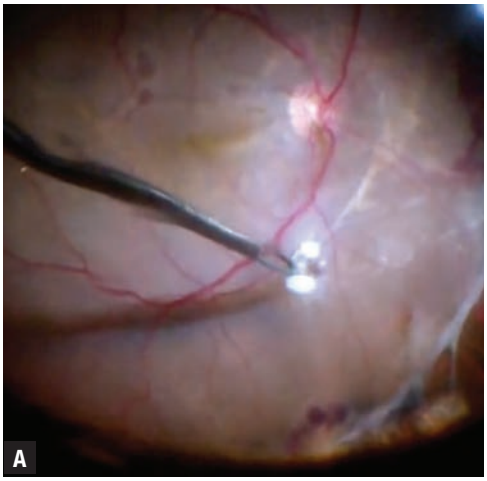
Dr. Hahn is a consultant to DORC.

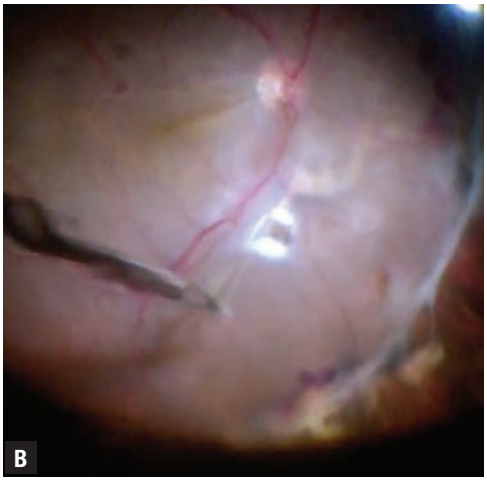
Subretinal proliferation is a well-known component of proliferative vitreoretinopathy and has been reported to occur in 15 to 47 percent of eyes with a retinal detachment.[1-4] The vast majority of subretinal proliferation occurs in the form of diffuse sheets underneath the retina and is mainly composed of glial tissue. Due to a relative lack of collagen in glial cells, this sheet of tissue rarely contracts and seldom prevents retinal reattachment during surgery.[5]

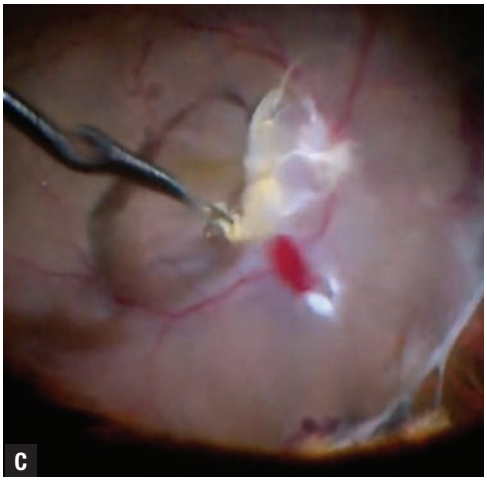
In contrast, subretinal bands have been shown to contain differentiated pigment epithelial cells that contain myofibroblasts.[2] These cells initially grow as membranes beneath the retinal surface. With expansion under the contractile force of the myofibroblasts, breaks eventually occur in these membranes, leading to the formation of branching subretinal bands.[5] These bands can create a contractile force on the retina, preventing retinal reattachment during surgery.[6]

Dealing with taut bands

In 13 to 28 percent of patients with subretinal bands, the retina remains taut despite appropriate maneuvers, requiring the bands to be excised to achieve proper anatomical success.[6-7] Once you decide intraoperatively to remove the subretinal membranes, several







A) Subretinal band being grasped with forceps after the creation of an access retinotomy. The retinotomy was created with endocautery in an area where the band is thick and allows for good manipulation. B) The band is pulled tangentially 180 degrees away from the side of greatest adherence to avoid enlarging the retinotomy site. C) The subretinal band has been removed in one piece. Notice that the retinotomy site has largely retained its initial size thanks to maneuvers we discussed.

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techniques can ease the process.

First, if the subretinal band is adjacent to a preexisting retinal break, a retinotomy might not be required. With the use of a pic, a loop of the subretinal band can be brought through the existing retinal break and removed with intraocular forceps.[7]

However, if a retinotomy is needed to get access to the band, it should be made in a location that maximizes this access. To allow greater leverage on the band, the retinotomy needs to be made at a site where the band is thickest and the angle at which the forceps enter the subretinal space should be considered.

Take care to ensure the band itself isn't severed during the creation of the retinotomy because the contractile force will cause the band to retract, which will prevent proper removal. Placing the retinotomy slightly adjacent to the band rather than directly over it will reduce the risk of making this crucial error.

Ways to remove the band

Once the subretinal space has been accessed, the band can be removed in several ways. One way is to grasp the band with serrated intraocular forceps and pull it tangential to the retina to avoid enlarging the retinotomy or causing further damage.[8]

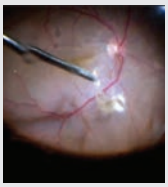
Alternatively, swiveling the forceps to wrap the band around them or using chandelier illumination and a hand-over-hand technique with two forceps have also been shown to be successful.[7]

If the band is strongly attached to the underlying retinal pigment epithelium, preventing proper removal, cutting the band in several places to release the traction can provide enough flexibility to allow for reattachment.[7]

Rarely, if a diffuse sheet of subretinal proliferation requires removal, it may become prudent to make an extensive peripheral retinotomy and turn the retina over to grasp the tissue under direct visualization.[8]

View the Video

Watch as Drs. Reddy and Patel remove a thick subretinal PVR band. Available at https://bit.ly/VideoPearl_024



Bottom line

The anatomical success in cases that require subretinal band removal matches that of PVR cases that require no SRM removal. While it's rare to have subretinal bands that require removal, a proper understanding of the pathophysiology combined with the appropriate technique can help ensure surgical success and ease the removal of subretinal bands.

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hAM plug for macular holes

(Continued from page 12)

blood have been reported, but with associated intraoperative and postoperative complications.[10] Similarly, neurosensory retinal free flap transplantation can be challenging; the most appropriate size of the neurosensory free flap is unclear, as it may contract after being implanted into the macular hole.[11]

Bottom line

Overall, we think the use of hAM plugs is a promising new way to treat large macular holes. When combined with MHH, this technique may offer good anatomical closure rates and visual recovery.

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UPDATE ON DRUG DELIVERY

A closer look at emerging drug-delivery platforms

An update on Port Delivery System with ranibizumab, a large-molecule anti-VEGF candidate and subretinal gene therapy to treat neovascular AMD.

Matthew Karl, MD

Matthew Ohr, MD

By Matthew Karl, MD, and Matthew Ohr, MD

Take-home points

- The advent of anti-VEGF therapy has revolutionized the treatment of neovascular age-related macular degeneration. However, the need for frequent monitoring and treatment places a significant burden on patients and their families.
- The Port Delivery System with ranibizumab is a novel reservoir device that's surgically implanted in the pars plana to allow continuous passive diffusion of anti-VEGF into the vitreous.
- Higher-molecular weight molecules may potentially decrease the frequency of intravitreal injections.
- Subretinal gene therapy, which has emerged as a treatment for other retinal diseases, may hold promise for the treatment of nAMD.

Bios

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DISCLOSURES: Dr. Karl has no financial disclosures.

Dr. Ohr has received research grants from Apellis, Genentech/Roche, Novartis and Regeneron Pharmaceuticals. He owns stock in Alimera Sciences, and serves as a consultant to and holds equity in Vitranu.

Anti-VEGF agents have revolutionized the treatment of neovascular age related macular degeneration, but, as retina specialists know all too well, real-world outcomes have fallen short of those seen in clinical trials in part due to the burden of frequent monitoring and treatment on patients and their families.[1]

Reducing this treatment burden and replicating the visual outcomes reported in clinical trials remains a major unmet need. Active areas of research to solve this problem include port delivery systems, high-molecular weight anti-VEGF antibody conjugates, subretinal gene therapy and others. Here, we review some potential future therapies that may mitigate or obviate the need for intravitreal injections in the future.

PDS with ranibizumab

Port Delivery System with ranibizumab (PDS, Genentech/Roche) is a permanent, refillable, surgically implanted drug delivery system that allows continuous delivery of a novel formulation of ranibizumab into the vitreous cavity by passive diffusion (*Figure 1*).[2] The Food and Drug Administration last month accepted Genentech's Biologics License Application under priority review for PDS, and issued an expected approval date by October 23.

In the Phase II Ladder clinical trial, 220 patients with newly diagnosed treatment-responsive nAMD were randomly assigned to treatment with the PDS with ranibizumab 10 mg/ml, 40 mg/ml, or 100 mg/ml, or to monthly intravitreal ranibizumab 0.5-mg injections (Lucentis, Genentech/Roche).[2]

The primary efficacy endpoint was time to first implant refill. The 100-mg/ml PDS group demonstrated the longest time to implant refill—the median time for implant refill in the PDS 10-, 40 and 100-mg/

mL arms was 8.7, 13 and 15.8 months, respectively—although the study wasn't powered to detect a statistically significant difference between the 40- and 100-mg/mL arms.

The proportion of patients who didn't require an implant refill for at least 12 months was 28.9, 56 and 59.4 percent in the PDS 10-, 40- and 100-mg/ml arms, respectively. Patients were treated with rescue therapy with ranibizumab 0.5 mg intravitreal injection in cases where predefined criteria weren't met. Rescue therapy was required in 22.4, 4.8 and 1.7 percent of the 10-, 40- and 100-mg/mL arms, respectively.

Secondary Ladder Outcomes

Secondary efficacy outcomes included change in visual function and central foveal thickness. The adjusted best-corrected visual acuity from baseline at 22 months was –4.6, –2.3, +2.9 and +2.7 Early Treatment Diabetic Retinopathy Study letters for the 10-, 40- and 100-mg/mL PDS patients, and monthly 0.5-mg intravitreal ranibizumab injections patients, respectively. A post hoc analysis showed visual outcomes between the 100-mg/mL PDS group and the monthly 0.5-mg intravitreal ranibizumab group were comparable.

Importantly, the patients in this trial were noted to be responsive to anti-VEGF prior to enrollment, and so most had excellent vision at baseline. A dose response was similarly seen for anatomical outcomes. The adjusted change in central foveal thickness from baseline at 22 months was –0.7, –20.9, –4.0, and –10.9 µm for the 10-, 40- and 100-mg/mL PDS patients and monthly 0.5-mg intravitreal ranibizumab injections patients, respectively.

High rates of vitreous hemorrhage early in the trial initially prompted a pause in enrollment. Once the incision site at the pars plana was identified as the likely site of hemorrhage, the surgical procedure was modified to include laser ablation of the pars plana, reducing the incidence of vitreous hemorrhage from 50 to 5 percent.[2]

PDS Archway Trial

The Archway study is a Phase III randomized clinical trial of 418 patients comparing the PDS to ranibizumab. In the experimental arm, patients received ranibizumab delivered through the PDS implant with 100-mg/mL with refill-exchanges at fixed 24-week intervals. In the comparator arm, patients receive monthly injections of ranibizumab 0.5 mg. Initial results presented at the American Society of Retina Specialists annual meeting last year showed that 98.4 percent of PDS patients were able to last six months without needing additional injections and achieved visual acuity outcomes equivalent to patients receiving ranibizumab injections every four weeks.[3]

More details of the Phase III Archway trial of PDS with ranibizumab appear on page 29 in this issue.

The Portal study (NCT03683251) is an extension study of Ladder and Archway that will enroll 1,000 patients who will receive PDS 100 mg/mL with refill-exchanges administered every 24 or 36 weeks for approximately 144 weeks. The estimated

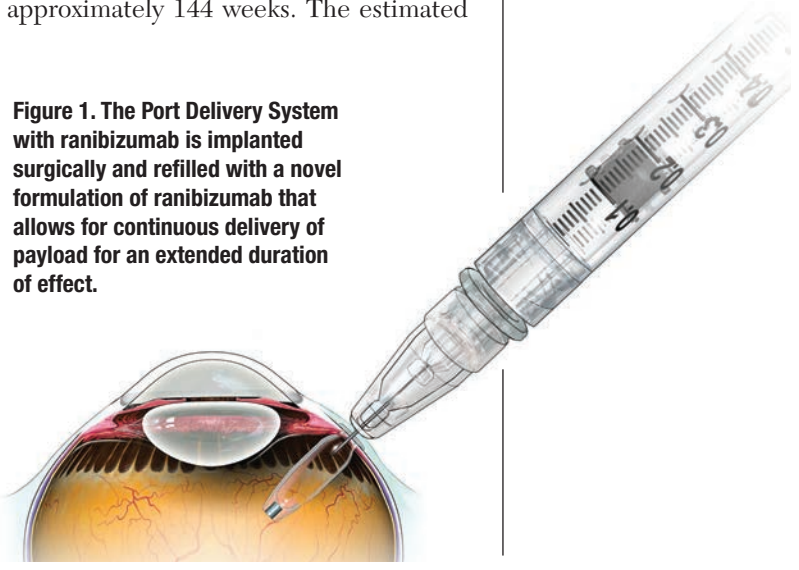

Figure 1. The Port Delivery System with ranibizumab is implanted surgically and refilled with a novel formulation of ranibizumab that allows for continuous delivery of payload for an extended duration of effect.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

6,250 PATIENT CHARTS

Inspired by a real patient with DME.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

TRUST THE #1 PRESCRIBED ANTI-VEGF FDA APPROVED FOR WET AMD, DME, AND MEfRVO*

*IBM Truven MarketScan data: number of injections administered from Q4 2018 through Q3 2019; Data on file.

Proven first-line efficacy

- **Powerful efficacy** and **robust anatomic outcomes** across all indications as shown in phase 3 clinical trials[1-8]
- A broad range of indications and **dosing flexibility** across several FDA-approved indications[1]

Demonstrated safety profile

- **Demonstrated safety** profile across 4 VEGF-driven retinal diseases: Wet AMD, DR, DME, and MEfRVO[1]

A legacy of clinical experience

- **9 years** of extensive real-world experience[1]
- **≈13 million** doses administered to **>1 million** eyes since launch (and counting)[9]

EYLEA® (aflibercept) Injection 4 U℠

A COMPREHENSIVE PATIENT SUPPORT PROGRAM TO HELP FACILITATE ACCESS TO EYLEA

- 82% of payers offer access to EYLEA first line, covering **>272 million** patients[9,†]
- As of June 30, 2020, EYLEA4U® has provided **>4.4 million** total support services to eligible patients prescribed EYLEA[9]

†Data represent payers across the following channels: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

DISCOVER WHAT ELSE YOUR PATIENTS COULD SEE WITH EYLEA AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

03/2021
EYL.21.02.0021

EYLEA® (aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use
The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052

study completion date is July 2026.

KSI-301

While PDS provides continuous delivery of anti-VEGF, other methods of increasing the intraocular availability of anti-VEGF are being investigated. Large molecules are more stable and have longer intravitreal half-life.[4] One such molecule, KSI-301 (Kodiak Sciences) is a novel anti-VEGF biologic built on an antibody biopolymer conjugate platform that's designed to extend availability of the molecule in the eye by increasing its molecular weight (*Figure 2*).[4,5] It's administered as an intravitreal injection and is designed to provide sustained inhibition of VEGF for as long as six months.

DAZZLE (NCT04049266) is an ongoing Phase IIb/III randomized study designed to evaluate the efficacy, durability and safety of KSI-301 in patients with treatment-naïve nAMD. The trial enrolled 550 patients randomized 1:1 to receive either KSI-301 5 mg at 12, 16 or 20 months as specified in the study protocol, or aflibercept 2 mg once every four weeks for three months followed by once every eight weeks.

The primary outcome is mean BCVA and topline results are expected early next year. An earlier Phase I study (NCT03790852) resulted in visual improvements with a six-month interval of IVT in patients with nAMD along with other retinal vascular diseases.[4]

RGX-314

Subretinal gene therapy involves delivery of a viral vector to the subretinal space during vitrectomy. Once viral transduction occurs, the target host cells transcribe and translate the genetic material into proteins. Subretinal gene therapy has been shown to be effective in the treatment of RPE65-mediated inherited retinal dystrophy, for which voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) received FDA approval.[6] Gene therapies are currently in development for choroideremia and X-linked retinoschisis.

RGX-314 (RegenxBio) is a recombinant adeno-associated virus (AAV) gene therapy vector carrying a coding sequence for a soluble anti-VEGF protein (*Figure 3, page 26*). Delivery of this protein into the subretinal space during vitrectomy as a one-time therapy could potentially reduce the treatment burden of currently available therapies while maintaining vision.

A Phase I/IIa, open-label, multiple-cohort, dose-escalation study is under way and is expected to conclude in this summer (NCT04049266). The primary endpoint is safety at 26 weeks. Secondary endpoints, assessed at 106 weeks, include change in BCVA, change in central retinal thickness, mean number of rescue injections and mean

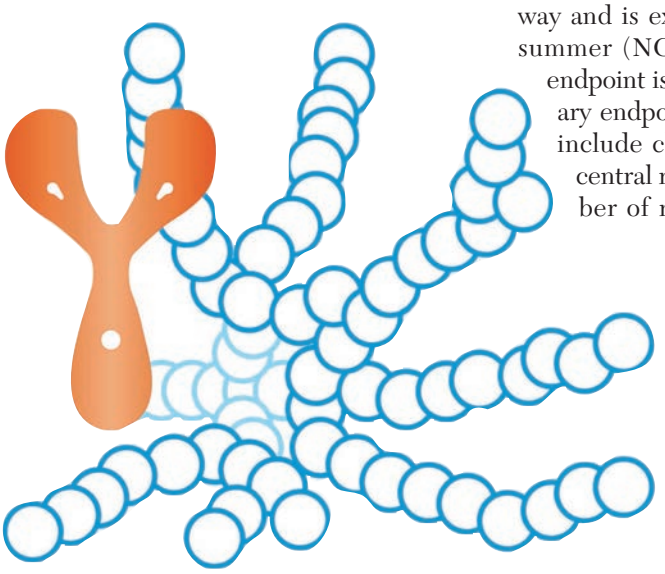

Figure 2. KSI-301 is a novel anti-VEGF biologic built on an antibody biopolymer conjugate that uses molecular weight to extend the durability of anti-VEGF effect. The Y-shaped neuron represents the antibody and the blue and white structure the biopolymer.

In gene therapy, once viral transduction occurs, the target host cells transcribe and translate the genetic material into proteins.

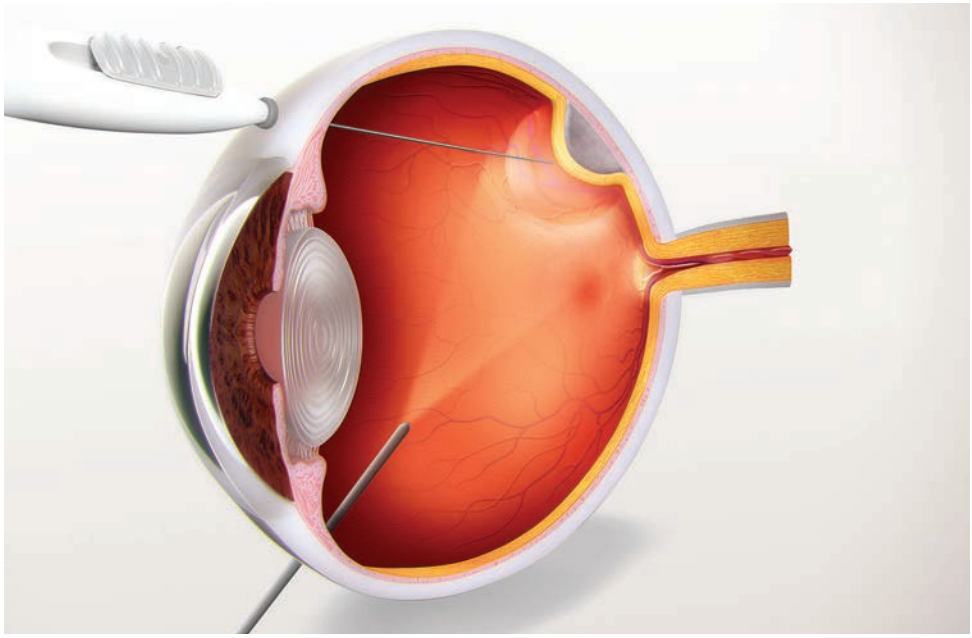

Figure 3. RGX-314, delivered as a onetime subretinal injection, as demonstrated in this illustration, is a recombinant adeno-associated virus gene therapy vector carrying a coding sequence for an anti-VEGF protein.

The burden of anti-VEGF treatment means that real-world outcomes often fail to mirror clinical trial results. So there's a significant need to develop therapies that reduce the burden of frequent intravitreal injections.

change in area of choroidal neovascularization.[7]

Early data released by the company show treatment effect at three years, with four of six patients being injection-free from nine months to three years, and three of six patients being injection-free over three years.[8] ATMOSPHERE, a Phase IIb/III clinical study, will enroll 300 patients and evaluate two doses of RGX-314 with a primary endpoint of mean BCVA relative to ranibizumab (NCT04704921). The estimated study completion date is March 2024.

Bottom line

Anti-VEGF therapy is extremely effective at maintaining and, in some cases, improving BCVA in patients with nAMD. However, the burden of treatment means that real-world outcomes often fail to mirror clinical trial results. So there's a significant need to develop therapies that reduce the burden of frequent intravitreal injections. Several promising treatments in the pipeline may fundamentally change the treatment paradigm for nAMD as anti-VEGF therapies did and potentially provide better outcomes and improved quality of life for our patients.

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UPDATE ON DRUG DELIVERY

Retinal implant platforms moving from uveitis to AMD

Treatments show potential for various posterior-segment diseases based on their success treating noninfectious uveitis.

By Daniel F. Kiernan, MD, FACS

Daniel F. Kiernan, MD, FACS

Take-home points

- Extending the duration of treatment for posterior-segment disease may alleviate patient burden.
- The fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq, EyePoint Pharmaceuticals) and the dexamethasone implant 0.7 mg (Ozurdex, Allergan/AbbVie) may be employed by clinicians seeking a nonsurgical option to extend treatment intervals for patients with noninfectious uveitis affecting the posterior segment.
- The Port Delivery System with ranibizumab (PDS, Genentech/Roche) is an investigational drug/device that has shown potential for extending treatment intervals in patients with neovascular age-related macular degeneration.
- PDS and other emerging emerging treatments for nAMD follow in the tradition of surgically implanted devices that may address the unique dynamics of a patient population with a heterogenous response to therapy.

Noninfectious uveitis affecting the posterior segment remains one of the most confounding diseases that retina specialists treat, due in large part to the heterogeneous presentations and responses to therapy. Innovations in uveitis treatment have given clinicians more options, and the adoption of office-based therapies, such as the fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq, EyePoint Pharmaceuticals) and the intravitreal dexamethasone implant 0.7 mg (Ozurdex, Allergan/AbbVie), have eased the burden on patients and decreased the risks associated with surgery.

Innovations in implant technology and sustained-release drug formulations don't stop there. Surgical implant technology is making its way into treatments for neovascular age-related macular degeneration. These wet AMD drug candidates have followed the framework for sustained-release drug therapy that investigators first explored in the uveitis treatment pipeline.

A new concept for uveitis therapy emerges

Retina and uveitis specialists have used implant therapies that slowly elute drug to reduce treatment burden since 2008, when the fluocinolone acetonide intraocular implant 0.59 mg (Retisert, Bausch + Lomb) was shown to be safe and effective for noninfectious uveitis of the posterior segment (NIU-PS).[1] David G. Callanan, MD, and colleagues demonstrated the safety and efficacy of Retisert, which is surgically implanted, in 2008.[1]

In their study, they implanted Retisert at one of two doses (0.59 or 2.1 mg) in 278 patients and compared results at one, two and three years to patients who received no implant. As might be predicted with a steroid implant, patients in the treatment arms had higher rates of intraocular pressure-lowering surgery and cataract

Bio

Dr. Kiernan is a vitreoretinal surgeon with The Eye Associates in Sarasota, Florida.

DISCLOSURES: Dr. Kiernan is a speaker and consultant for, and receives grant support from EyePoint Pharmaceuticals.

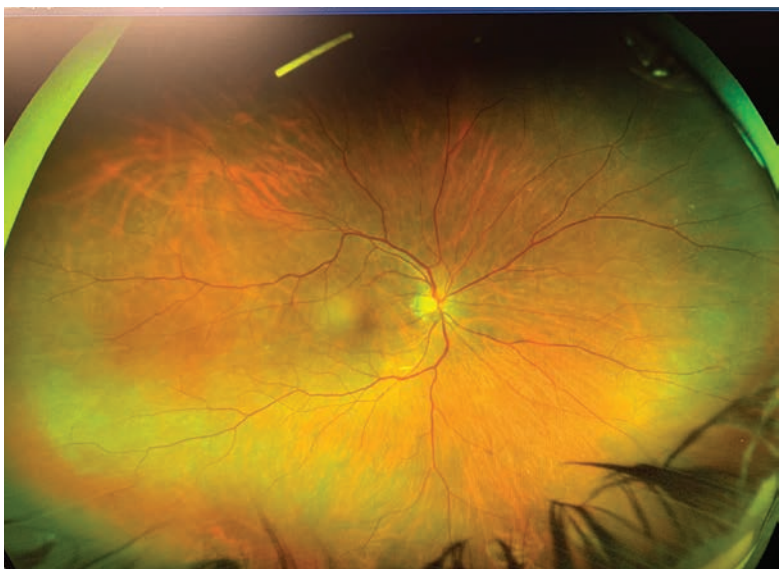
surgery. Still, reduction in recurrence rates at all three were statistically significant. The rates of recurrence were similar among both treatment arms, and the lower dose was eventually submitted for Food and Drug Administration approval.

One major barrier to treatment with Retisert is the surgery required to implant the device. Some patients with NIU-PS may not be suited for surgery, and others may not want to accept the risks associated with it. Starting in 2010, clinicians and patients had a new steroid-based option for the treatment of uveitis that didn't require surgery.

Dexamethasone implant

A single, multicenter, randomized study of 153 patients with NIU-PS assessed the safety and efficacy of Ozurdex.[2] Vitreous haze (VH) scores were examined at eight weeks in patients who received Ozurdex or sham. At that time point, 47 percent of patients in the treatment group had VH scores of 0 (i.e., no uveitis) compared with 12 percent of patients in the sham group. The difference was statistically significant.

Ozurdex has a treatment effect of three to four months, which may be appropriate for some patients with NIU-PS. Still, clinicians and patients alike may find a longer treatment interval desirable.



The fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq, EyePoint Pharmaceuticals) can be observed at the 12 o'clock position in the posterior segment.

Extended-duration, nonsurgical option

Clinicians seeking an extended-duration, nonsurgical therapy that lasts longer than Ozurdex may turn to Yutiq, which is administered in a clinical setting and remains in the posterior segment (*Figure*). The three-year results of a pivotal Phase III trial assessing the safety and efficacy of Yutiq for the treatment of NIU-PS found that at month 36, patients who received Yutiq had significantly fewer uveitis recurrences compared with those who received sham injection, plus standard therapies as needed (66 vs. 98 percent, $p < 0.001$).[3]

Time to first recurrence of uveitis was 657 days in the Yutiq arm compared with 71 days in the sham arm ($p < 0.001$), and the mean number of recurrences in the Yutiq arm (1.7) was significantly lower than in the sham (5.3; $p < 0.001$). Among patients who received Yutiq, 58 percent received adjunctive treatment during the 36-month study period compared with 98 percent of sham-treated patients.

The rate of IOP-lowering surgery in the sham-treated group (12 percent) was double that of the Yutiq group (6 percent). Rates of cataract surgery were higher in the Yutiq group (74 percent) than the sham group (24 percent).

Use of Yutiq in patients with NIU-PS could potentially reduce treatment burden by obviating the need for surgical administration and reducing the frequency of adjunctive anti-inflammatory therapy, both of which may be associated with other therapies. In my experience, Yutiq has been effective at treating NIU-PS while reducing treatment burden associated.

Implants in wet AMD

The evolution of treatments for NIU-

PS—from a surgically implanted device to a short-term in-office implant to a long-term in-office implant—demonstrates how innovators develop solutions that address real-world patient concerns and help maintain therapeutic drug levels over a longer duration. As wet AMD therapies move toward extended duration and surgical solutions, we can observe the continuance of this pattern of need-based improvement.

The Phase III Archway trial assessed the safety and efficacy of the Port Delivery System with ranibizumab (PDS, Genentech/Roche) in patients with wet AMD. PDS is a surgically implanted device that slowly releases a customized formulation of ranibizumab. The PDS can be refilled during a process known as a refill-exchange. During a refill-exchange, a syringe clears any unused portion of drug from the implant and refills the implant with a new batch of customized ranibizumab.

The Archway investigators found that the PDS with ranibizumab was noninferior to monthly ranibizumab injections.[4] As of February, about 80 percent of Archway patients reached 72 weeks.[4] Among those patients, the average number of injections in the PDS arm and the monthly ranibizumab arm was 3.9 and 19.5, respectively. These data suggest that the PDS may be an option for extending treatment duration in patients with wet AMD and reducing injection burden.

The similarities between Retisert and the PDS could foretell the future of extended-duration treatment for wet AMD. In a sense, their *raisons d'être* are similar. They were designed to address real-world issues in a chronic disease, in patient populations with variable responses to therapy who may require frequent treatment. Looking at the wet AMD pipeline, we can anticipate similar progress in long-term therapy, from surgically implanted drug reservoirs to simpler in-office treatments.

Bottom line

Office-based therapies that extend treatment intervals for patients with NIU-PS offer the opportunity to reduce barriers to treatment and increase quality of life for patients. It remains to be seen how the lessons learned in uveitis therapy will also apply to wet AMD therapy as technology in that arena advances. RS

Candidates in the pipeline

The pipeline has a number of promising candidates that could extend treatment intervals for patients with wet age-related macular degeneration. Three of them are:

- **OTX-TKI (Ocular Therapeutix).** This tyrosine kinase inhibitor (TKI) is a bioresorbable hydrogel fiber implant delivered via intravitreal injection. A Phase I trial is expected to be completed in November (NCT03630315). As of May, no adverse events have been reported in patients in the Phase I study.[5]
- **EYP-1901 (EyePoint Pharmaceuticals).** Another bioerodible TKI candidate, also administered via intravitreal injection, EYP-1901 is under investigation for wet AMD therapy in a Phase I study scheduled to be completed in April 2022 (NCT04747197).
- **GB-102 (Graybug).** This proprietary microparticle depot formulation of sunitinib malate that's delivered via intravitreal injection is the subject of the Phase IIb ALTISSIMO trial in wet AMD. Topline results from the trial showed that the first time to supportive therapy for patients who received 1 mg sunitinib was five months.[6] The drug has been well tolerated to date.

The evolution of treatments for non-infectious uveitis of the posterior segment demonstrates how innovators develop solutions that address real-world patient concerns and help maintain therapeutic drug levels.

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Using OCT to evaluate fluid in non-neovascular AMD

How optical coherence tomography, OCT angiography and fluorescein angiography can help direct diagnosis and treatment decisions.

Karen Jeng-Miller, MD

By Karen Jeng-Miller, MD

Take-home points

- While fluid is the hallmark of neovascular age-related macular degeneration, fluid can be present in cases of non-neovascular AMD.
- Optical coherence tomography, OCT angiography and fluorescein angiography can help verify the presence of a choroidal neovascular membrane and thus inform diagnosis and treatment decisions.
- It's important to recognize that fluid is not always a sign of neovascular activity, a differentiation that's important for treatment decisions.
- Careful evaluation of non-neovascular AMD with fluid is critical to determine the optimal treatment paradigm and minimize the treatment burden on patients and the health-care system.

Non-neovascular or nonexudative, or dry, age-related macular degeneration is defined as the presence of drusenoid deposits detected via clinical exam or ocular coherence tomography, without any associated choroidal neovascular membrane (CNVM). Drusen are characterized by extracellular debris that deposit between the retinal pigment epithelium and Bruch's membrane.

While anti-VEGF therapy has revolutionized the treatment strategies and visual outcomes in patients with neovascular AMD, currently no Food and Drug Administration-approved treatments exist for visual decline in non-neovascular AMD.

The science of fluid in dry AMD

While subretinal (SRF) or intraretinal fluid (IRF) are established as indicators of neovascularization in AMD, it's becoming increasingly evident that fluid may be present in cases of non-neovascular AMD. Thus, it's important to recognize that fluid isn't always a sign of neovascular activity. This differentiation is important for treatment decisions.

One hypothesis regarding this nonexudative fluid states that it may be due to transudative mechanisms, such as disrupted Müller cells or retinal pigment epithelial pump failure.[1] Cystoid, or cavitary, spaces can occur over areas of atrophy as a result of the retinal degeneration process, possibly secondary to Müller cell degeneration (*Figure 1*).[2]

Mechanical strain from confluent drusen can also result in the appearance of SRF. In these cases, when confluent drusen are accompanied by subretinal spaces that appear filled with fluid, distribution of the fluid in the area between adjacent drusen may indicate that the group of coalescent drusen creates mechanical strain

Bio

Dr. Jeng-Miller is a graduating vitreoretinal surgery fellow at Tufts University/Ophthalmic Consultants of Boston, with an appointment as an assistant professor in the department of ophthalmology and visual sciences at the University of Massachusetts Medical School, Worcester.

DISCLOSURES: Dr. Jeng-Miller has no relevant financial relationships to disclose.

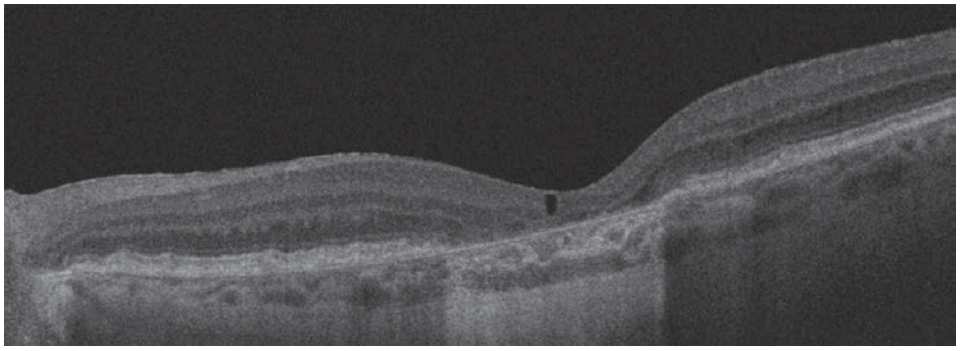

Figure 1. Optical coherence tomography demonstrates an area of subfoveal atrophy in a case of non-neovascular age-related macular degeneration with overlying cystoid degeneration.

on the outer retinal layers, pulling the sensory retina away from its position.[3]

A 2020 study examined three different patterns of subretinal fluid in non-neovascular AMD that progress to collapse and atrophy:[1]

- fluid at the apex of a large drusenoid pigment epithelial detachment;
- fluid at the crypt between confluent drusen; and
- low-lying drape of fluid over confluent drusen (*Figure 2, page 32*).

As a result, distinguishing between fluid that's secondary to neovascular or non-neovascular processes is critical for making appropriate treatment decisions and avoiding unnecessary anti-VEGF therapy.

The role of OCT and FA

OCT has become a critical tool in the diagnosis and evaluation of AMD. Drusen can sometimes be very subtle during a clinical exam. OCT helps to visualize and evaluate these fine drusen so disease classification and management can proceed. If an OCT image reveals no associated fluid, it's more likely that a CNVM isn't present and further ancillary testing is unnecessary.

Concern for SRF or IRF increases the possibility of a CNVM. Fluorescein angiography is helpful in confirming the presence of a CNVM, thus informing the diagnosis and treatment recommendation. Performing FA may not only be confirmatory, but may also help the patient understand the need for treatment, which is particularly valuable given the hesitance and concerns that may exist regarding intraocular injections.

While the risks for serious complications related to anti-VEGF therapy are low, the time and psychological burdens on the patient are significant. When a patient understands more about their disease process, it may help with treatment receptivity.

OCT angiography has also become a useful tool in evaluating the presence of a CNVM. Often, CNVM can be seen on the *en face* OCTA or flow can be present on the B-scan, suggesting the presence of a CNVM.

However, limitations in OCTA often lie in projection artifacts. As the technology improves, it's likely this method of imaging will become more widely employed in daily diagnostic questions.

Diagnostic strategies and challenges

In differentiating between non-neovascular and neovascular AMD, it's important to look at the entire clinical picture: clinical exam; ancillary imaging; and patient subjective complaints.

On examination, the presence of a gray-

Drusen can sometimes be very subtle during a clinical exam. OCT helps to visualize and evaluate these fine drusen, which allows disease classification and management to proceed.

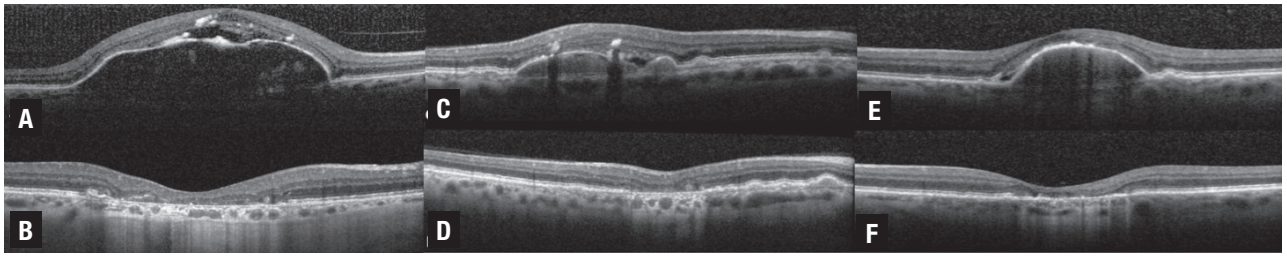

Figure 2. Three cases of non-neovascular age-related macular degeneration illustrating drusenoid pigment epithelial detachment (PED) and drusen associated with three different patterns of subretinal fluid (SRF) that progress to collapse and atrophy.[1] A) Spectral-domain optical coherence tomography illustrates drusenoid PED with crest of SRF associated with an acquired vitelliform lesion and focal retinal pigment epithelium thickening, including intraretinal hyper-reflective foci. B) At the five-year follow-up visit, the drusenoid PED is collapsed with development of complete RPE and outer retinal atrophy (cRORA). C) SD-OCT illustrates drusenoid PED with SRF located at the angle or crypt of the PED. D) At the 10-month follow-up visit, the PED is collapsed with progression to cRORA. E) SD-OCT illustrates drusenoid PED with low-lying drape of SRF. F) At the seven-year follow-up visit, the drusenoid PED is collapsed with progression to cRORA. (*Figure courtesy Assaf Hilely, MD. Reprinted with permission BMJ Publishing Group*)

Not all subretinal fluid is bad. Cases of persistent or residual SRF accompanied by better visual acuity have been reported, thus suggesting a functioning, albeit impaired, retinal pigment epithelium pump.

ish subretinal elevation or hemorrhage can point you toward a diagnosis of CNVM. It's also important to ascertain whether or not these patients have symptoms, such as distortions, new blind spots or any other change in vision. These findings, in conjunction with OCT, and possibly OCTA and FA testing, can help determine the true etiology of the fluid and guide treatment options.

Not all SRF is bad

Remember that not all SRF is bad. Cases of persistent or residual SRF accompanied by better visual acuity have been reported,[4] thus suggesting a functioning, albeit impaired, RPE pump.[5] This is in contrast to cases of RPE and outer retinal atrophy without fluid with accompanying poor vision where fluid is cleared by passive mechanisms due to the absence of the normally functioning RPE and outer retinal barriers.[5]

When the findings aren't definitive, it's important to discuss treatment options with the patient, including the possibility of a trial injection and follow-up assessment. This strategy mitigates unnecessary treatment burden while avoiding the risks associated with no treatment or loss to follow-up, resulting in vision loss.

Bottom line

Non-neovascular AMD with SRF is an increasingly recognized entity that can be difficult to distinguish from nAMD. Intravitreal injection therapy for nAMD has revolutionized the treatment paradigm, but the time, cost and psychological burdens on the patient aren't insignificant.

So, it's important that physicians are aware that fluid may be present in non-neovascular AMD and avoid reflexive unnecessary anti-VEGF therapy. The use of OCT, OCTA and FA to verify the presence of a CNV membrane becomes increasingly important in helping to differentiate these entities and guiding patient management.

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RETINA STANDOUTS FROM ARVO

Five emerging treatments show mixed results

Uncertainty about PVL for VMT and aflibercept for NPDR, some clarity on PDT, and early promise for stem cells and a bioresorbable implant.

By Ashkan M. Abbey, MD

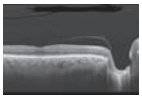
Ashkan M. Abbey, MD

Take-home points

- In-office pneumatic vitreolysis for symptomatic vitreomacular traction resulted in a high rate of retinal tear or detachment.
- Two-year results of aflibercept for nonproliferative diabetic retinopathy showed mixed results.
- Half-dose photodynamic therapy seemed better than oral eplerenone for chronic central serous chorioretinopathy.
- Allogenic human retinal progenitor cells showed potential for preserving photoreceptors in retinitis pigmentosa.
- A bioresorbable tyrosine kinase inhibitor implant showed sustained efficacy signals for neovascular age-related macular degeneration.

This year's virtual ARVO 2021 meeting brought together the best researchers in retina to exhibit the latest in diagnostics, treatment, and management strategies for retinal disease. Every year, ARVO distinguishes itself from other ophthalmology meetings due to its inclusion of a broad spectrum of research—from innovative basic science to the latest clinical trials.

Here, we report on five compelling presentations in retina: results of DRCR.net Protocols AG, AH and W; the efficacy of half-dose photodynamic therapy vs. oral eplerenone for central serous chorioretinopathy; allogenic human retinal progenitor cells for retinitis pigmentosa; and intravitreal axitinib for neovascular age-related macular degeneration.



DRCR.net Protocols AG and AH

Previously published retrospective case series demonstrated the efficacy of in-office pneumatic vitreolysis (PVL) for symptomatic vitreomacular traction (VMT) and VMT with associated full-thickness macular hole (FTMH). DRCR Research Network Protocols AG (symptomatic VMT) and AH (VMT with associated small FTMH) were the first prospective trials to evaluate PVL in these eyes.

Protocol AG was a randomized, controlled trial that included eyes with VMT ≤3 mm in width on optical coherence tomography. It excluded eyes with lamellar or full-thickness macular holes. Best-corrected visual acuity ranged from 20/32 to 20/400. Forty-six eyes were randomized to receive either PVL (IVT injection of 0.3 mL of 100% C3F8) or sham injection. Patients were seen at one, four, 12 and 24 weeks post-injection. Rescue vitrectomy was recommended if their vision decreased from baseline by ≥5 letters at two consecutive visits (beginning at week 4) or by 10 letters or more from baseline at any visit.

Seventy-eight percent of PVL eyes

Bio

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

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

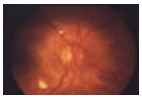
achieved VMT release without the need for rescue vitrectomy, compared to just 9 percent of sham ($p < 0.0001$). At 24 weeks, BCVA didn't significantly improve in the PVL group vs. sham. However, the PVL group did exhibit a significant reduction in loss of ellipsoid zone integrity (27 percent vs. 50 percent in sham, $p < 0.009$). One eye in each group developed a FTMH.

Protocol AH included eyes with VMT ≤3 mm in width on OCT and associated small FTMH ≤250 µm. BCVA ranged from 20/25 to 20/400. Mean macular hole diameter was 79 µm. Thirty-five eyes were randomized to receive either PVL (IVT injection of 0.3 mL of 100% C_3F_8 followed by four days of face-down positioning for half of each day) or sham injection. Patients were seen at one, four, 12 and 24 weeks postinjection. Rescue vitrectomy was recommended if the macular hole diameter didn't improve after four weeks. Twenty-nine percent of eyes receiving PVL achieved macular hole closure, and 34 percent required rescue vitrectomy. Mean baseline visual acuity improved from 20/80 to 20/50 with PVL.

Unfortunately, PVL resulted in retinal tear or detachment in 12 of the treated eyes compared to none of the sham eyes. Due to these safety concerns, the steering committee decided to terminate these trials early.

Both studies demonstrated encouraging efficacy of PVL for the treatment of VMT and VMT-associated FTMH, but the risks of retinal tear and detachment appear to be unacceptable to most. PVL appears to be a somewhat effective treatment for VMT, but, because of its potential safety issues, it should be limited to patients with significant contraindications for surgery.

Lead author Clement K. Chan, MD, reports commercial relationships with Allergan/AbbVie, Amgen, Chengdu Kanghong Pharma, Iveric Bio, Regenerative Patch Technologies, Regeneron Pharmaceuticals and Genentech/Roche. Co-author Calvin Mein, MD, reports relationships with Apellis, Novartis, Regeneron and Amazon Smile.



DRCR.net Protocol W

There has been considerable debate among retina specialists regarding the treatment of patients with moderate to severe nonproliferative diabetic retinopathy. These patients are at high risk for developing vision-threatening complications, and a recent trend has emerged toward early treatment of these patients with IVT anti-VEGF injections, even if they don't have macular edema.

DRCR.net Protocol W aimed to determine if aflibercept (Eylea, Regeneron Pharmaceuticals) can prevent the development of PDR and center-involved diabetic macular edema over two years. It also aimed to determine if there was an associated visual benefit at four years.

This was a multicenter, prospective, randomized clinical trial in eyes with moderate to severe NPDR (ETDRS severity levels 43-53) without CI-DME. BCVA was 20/25 or better. Eyes were randomized to IVT aflibercept or sham at baseline, one, two and four months, followed by every four months through two years. For the next two years, the eyes would receive treatment only if the disease severity was worse than mild NPDR. Both groups received aflibercept with the development of PDR or CI-DME.

The study included 399 eyes: 200 in the aflibercept group and 199 in the sham group. At two years, the incidence of CI-DME was 15 percent in the sham group and 4 percent in the aflibercept group (hazard ratio [HR] 0.36). The incidence of PDR was 33 percent and 14 percent in the groups, respectively, (HR 0.34). The combined incidence of PDR or CI-DME was 16 percent in the treatment group and 44 percent in sham (HR 0.32).

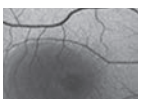
Although aflibercept reduced the incidence of vision-threatening complications, it didn't result in a significant difference in BCVA at two years. Also, central subfield thickness (CST) on OCT wasn't found to be significantly different at two years.

This study clearly establishes the efficacy of aflibercept for the improvement of DR.

Although aflibercept reduced the incidence of vision-threatening complications in eyes with moderate to severe NPDR, it didn't result in a significant difference in BCVA at two years.

However, the lack of visual benefit at two years makes it difficult to justify this approach for most cases of moderate to severe NPDR at this time. Frequent monitoring with dilated exam, OCT and widefield angiography is critical to ensure optimal outcomes for these high-risk patients. If a visual benefit is proven with the pending four-year data, this treatment for NPDR will likely be more widely adopted.

Lead author Raj K. Maturi, MD, reported commercial relationships with Allergan/AbbVie, Boehringer-Ingelheim, Genentech/Roche and Unity Biotechnology.



Oral eplerenone vs. PDT for CSCR

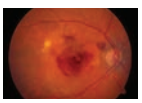
Due to a paucity of gold-standard evidence, consensus for treatment of chronic central serous chorioretinopathy (CSCR) remains lacking. The SPECTRA study was an open-label, multicenter, randomized controlled trial to compare the anatomic and functional efficacy and safety of primary treatment with either half-dose photodynamic therapy (PDT) or 25-mg oral eplerenone daily for a week, with or without crossover in patients with CSCR. Patients with fovea-involving subretinal fluid (SRF) persisting for more than six weeks and BCVA of 20/200 or better were randomized 1:1 to receive either half-dose PDT or oral eplerenone.

If SRF were present at the three-month follow-up, the patient would receive crossover treatment. In the primary oral eplerenone patients, 38 of 46 (82.6 percent) had persistent SRF and required crossover; 11 of 50 (22 percent) that received primary half-dose PDT required crossover. At the final follow-up visit 12 months after baseline, complete SRF resolution occurred in 38 of 39 (97.4 percent) patients with primary resolution after PDT; seven of seven in those with primary resolution after eplerenone; 30 of 35 (85.7 percent) in the eplerenone-to-PDT crossover group; and five of nine (55.5 percent) in the PDT-to-eplerenone crossover group. The researchers found no significant differences in BCVA and retinal sensitivity on microperimetry among the groups at the final visit.

This study demonstrated the superiority of half-dose PDT in the treatment of chronic CSCR, even after eplerenone treatment. CSCR remains one of the few indications for which I use PDT as a first-line therapy. It's reassuring to see randomized controlled trial data supporting this decision. Crossover to eplerenone in patients that had suboptimal treatment with PDT wasn't as likely to result in resolution of SRF. We need more data to determine the best treatment for this small subset of patients.

The study authors have no disclosures.

This study demonstrated the superiority of half-dose PDT in the treatment of chronic central serous chorioretinopathy, even after eplerenone treatment.



Allogeneic human retinal progenitor cells for RP

The use of stem cells and progenitor cells for a number of degenerative retinal conditions continues to advance. In this trial, patients with retinitis pigmentosa received an IVT injection of allogeneic human retinal progenitor cells (hRPC), which secrete neurotrophic factors that promote photoreceptor cell survival and function.

Eighty-four RP patients with BCVA of 20/80 to 20/800 were randomized to either a single injection of $3.0x10^6$ hRPC, $6.0x10^6$ hRPC or sham. Mean changes from baseline to month 12 were +2.81 letters in the sham group (n=26); +2.96 letters in the $3.0x10^6$ hRPC group (n=25); and +7.43 letters in the $6.0x10^6$ hRPC group (N=23).

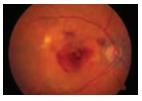
A post hoc analysis was performed in a subgroup that had baseline central fixation, no severely constricted field (≥12 degrees in diameter) in the study eye, and no significant difference in BCVA between the study and fellow eye (≤15 letters). In this subgroup, mean BCVA changes from baseline to month 12 were +1.85 letters in the sham group (n=13); -0.15 letters in the $3.0x10^6$ hRPC group (n=13); and +16.27 letters in the $6.0x10^6$ hRPC group (n=11; p = 0.003 for $6.0x10^6$ hRPC vs sham).

The $6.0x10^6$ hRPC group also showed

significant improvements in low-luminance mobility testing, contrast sensitivity, kinetic visual fields and visual function questionnaire VA LV VFQ-48 compared to sham. One treatment-related serious adverse event—ocular hypertension—was reported in the $3.0x10^6$ hRPC group. It was treated with antihypertensive therapy.

The neuroprotection of hRPC therapy may preserve photoreceptor survival while restoring function to certain photoreceptors that haven't fully degenerated. A primary advantage of this class of treatment is its ability to be gene agnostic; that is, it could theoretically be used for any of the mutations causing RP. The promising visual improvements and good safety profile in the $6.0x10^6$ hRPC subgroup with better initial BCVA will pave the way for a much anticipated Phase III trial in the coming year.

Lead author David Liao, MD, reports a commercial relationship with jCyte.



IVT axitinib implant for nAMD

Given the rapidly aging population, the need for greater durability to reduce the treatment burden for nAMD has become more pressing. OTX-TKI (Ocular Therapeutix), an IVT, bioresorbable, hydrogel-based implant, is designed to deliver the small-molecule tyrosine kinase inhibitor (TKI) axitinib in a sustained-release formulation to the vitreous, potentially extending treatment intervals in nAMD patients. TKIs have the potential for a broader anti-angiogenic profile than standard anti-VEGF agents.

This ongoing, prospective, Phase I study enrolled 20 patients with treatment-naïve or previously treated nAMD, separated into three treatment cohorts. IVT OTX-TKI was administered at doses of 200 µg (Cohort 1, n=6); 400 µg (Cohort 2, n=7); 600 µg (Cohort 3a, n=5/6); and 400 µg plus anti-VEGF induction therapy (Cohort 3b, n=2/6). Patients were assessed at days 0 (injection), 3, 7 and 14, followed by monthly assessments until the implants dissolved.

Preliminary results showed that BCVA and CST in Cohorts 1 and 2 remained relatively stable over the nine-to-12-month follow-up. Cohort 3 showed a sustained improvement in BCVA and CST over nine months of follow-up. In Cohorts 2 and 3, many eyes showed a decrease in CST and a clinically meaningful reduction in intraretinal and/or subretinal fluid by two months.

More than half of treated patients didn't need additional supportive anti-VEGF treatment at six months. Several patients in Cohort 2 demonstrated durability of therapy for up to 12 months. The implant biodegraded in all subjects in Cohort 1 in nine to 10.5 months. There were no dose-limiting toxicities, ocular serious adverse events, or infections.

Currently available anti-VEGF therapies permit treatment intervals of up to three months in certain patients. OTX-TKI was able to maintain an acceptable level of disease activity in a large proportion of this cohort of nAMD patients for up to six months without additional treatment. Of course, further study is warranted.

Lead author James Wong, MD, reports a commercial relationship with Ocular Therapeutix. Co-authors report relationships with Ocular Therapeutix, Allegro, Allergan/AbbVie, Genentech/Roche, Graybug, Novartis, Optistent, Placid0, Pr3vent and Regeneron Pharmaceuticals.

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The neuroprotection of human retinal progenitor cell therapy may preserve photoreceptor survival while restoring function to certain photoreceptors that haven't fully degenerated.

Department Editor *David R. P. Almeida, MD, PhDPhD*

Agency and advocacy in the digital world

How to utilize social media for patient advocacy and health promotion.

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

From their inception, online resources promised the opportunity to improve patient communication, unencumbered by the lackluster effectiveness of telephone and physical mail. Social media, as one of the cornerstones of modern digital media, can reach patients instantaneously beyond the limits of geography.

Although online platforms have their own drawbacks, some of which we've discussed previously, they nonetheless provide an immediate, facile means for targeted patient messaging to effect health promotion.

Role of agency and advocacy

Before we jump into online health promotion strategies, it's necessary to understand how health promotion can be achieved. Patient empowerment—agency and the ability to produce a particular effect—is a requisite. That is, patients must have the credible belief that they possess the necessary agency and ability to impact their respective outcomes.

As retina specialists, ophthalmologists and physicians at large, patient advocacy is our most effective route to foster patient agency. Clear communication and trustworthy rapport aid our advocacy efforts, whereas inconsistent messaging and pseudo-scientific inaction can irreparably harm it.

Let's use the COVID-19 vaccination as an example. Approximately 31 percent of U.S. adults are hesitant, reluctant or distrusting of the vaccines.[1] But widespread vaccination is critical to achieve herd immunity. Patient advocacy that's centered on the benefits of vaccination, honest dialogue on patient concerns regarding risks and the tactile removal of widespread disinformation are essential for energetic patient agency.[2]

Social media strategies

Continuing with our example, research shows vaccine-promoting organizations have faced obstacles using social media to reach audiences and measure impact. This has caused numerous missed opportunities to counter misinformation and connect with populations low in vaccine confidence.[3]

So, how do we as retina specialists improve our impact on patient health promotion via social media? On a larger scale, how can we as physicians build trust in vaccine safety and efficacy?

In answering these questions, it becomes salient that social media can improve outcomes by tailoring messages to specific groups, avoiding the repetition of false claims, adapting messaging in real-time as circumstances change, clearly responding to adverse events and identifying trusted messengers.[4]

Physicians have the opportunity to embrace the participatory nature of online platforms and improve patient reach—best done with credible content—to enhance engagement, education and effect.

Although medicine continues to be a slow adopter of online engagement, patient health promotion is an area where committing to the participatory nature of social media is critical to not losing our patient audience. If we're serious about our claims to positively impact health outcomes, then we must also be serious of our need to elevate patient agency with our advocacy efforts.

Bio

Dr. Almeida is a vitreoretinal surgeon at Erie Retinal Surgery in Erie, Pa.

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

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Is your 'new normal' compliant?

A compliance plan can be more than meeting a mandate. It can improve your operations. Here's a nuts-and-bolts approach.

By Ellen R. Adams, MBA

As we all move toward pandemic recovery, it's time to think about *how* to recover. Will you resume "business as usual" or try to reinvent your practice with improvements?

Of course, you want to emerge better and stronger. So, if you haven't done so already, consider implementing a compliance plan now. This may sound like a crazy idea. You may think a compliance plan is too much work, too much aggravation, not enough payback, not really needed and a huge waste of paper.

But consider this: Since the late 1990s, the Office of the Inspector General (OIG, a.k.a. the "Medicare Police") has published guidance for medical practices to develop a voluntary compliance program. The OIG stated that compliance program efforts "can also streamline and improve the business operations within the practice and therefore inoculate itself against future problems."[1]

Although not a guarantee against a Medicare allegation of fraud or abuse, the statement hints at the value of a compliance plan. When you develop, maintain and adhere to a robust compliance plan, you can point to it to support your intent to avoid fraud and abuse if you're the subject of a Medicare audit.

From suggestion to requirement

Rules change, however, and the OIG's guidance became a requirement in 2014. That year, the Affordable Care Act established the requirement that "a provider of medical or other items or services" shall establish a compliance program *as a condition of enrollment* [emphasis added] in Medicare, Medicaid, or the Children's Health Insurance Program (CHIP)."

Even if it weren't required, a compliance plan can bring many benefits to the practice. They include increasing the potential for proper claim submissions and a reduction in billing errors and, through the process, promoting patient safety and improving quality of care. Though not always a direct result, often a compliance plan can lead to improved revenue by reducing denials and appeals and, through correct coding, resulting in appropriate payment.

Only seven core elements

Although it can seem daunting to consider developing your compliance plan, the ACA has defined only seven core elements of an effective compliance program.[2] They are:

1. Written policies, procedures and standards of conduct for all employees. The material must be readily available to employees and reviewed by all employees within 90 days of hire, and annually thereafter.

Comment: Policies and procedures should be specific to your practice and address areas of vulnerability.

2. Compliance plan oversight by a designated compliance officer who reports directly to your practice leadership. The compliance officer is responsible for the day-to-day plan operations.

Comment: A viable option is to assign a team to monitor day-to-day activities, with your compliance officer managing those employees. This model allows you to assign the compliance officer position to an engaged physician.

3. Training and education of all employees—possibly the most important element of your compliance plan. In addition to new hire training and annual training, periodic refresher training is helpful to enforce your intention to maintain a compliant practice.

Comment: As part of your training, regular compliance reminders can be help-

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

Bio

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Your compliance plan needs to support your efforts to avoid fraud and abuse. If an OIG rep visits your office, all employees should be able to say where the plan is located and confirm that they've reviewed it.

ful. A short email on a regular schedule reminds employees of your compliance plan, policies and procedures and serves a wider purpose of enforcing your intention to avoid fraud and abuse. Reminders may include instruction on how to report a concern anonymously, "hot topics" in your billing department, or, assuming your plan is helping everyone submit clean claims, a congratulatory nod to everyone on successful audits.

4. Open lines of communication between all employees and the compliance officer. This should include an option for employees to report anonymously, in person or electronically. The compliance officer should answer all questions regarding compliance, routine and urgent, in a timely and appropriate manner.

Comment: The American Medical Association stresses the importance of an open-door policy for your compliance officer. The compliance officer shouldn't be feared, but be seen as a resource for all employees to help them navigate Medicare and other entity rules.

5. Auditing and monitoring to identify risks, measure effectiveness of the plan and ensure Medicare billing compliance. Auditing and monitoring should assure procedures are working properly and corrective actions implemented. Keeping a written record of audits is important. The audit process needs to be supported by policies and procedures to investigate and report misconduct.

Comment: You can train a staff member to perform audits or hire an external company; the auditor must be independent and competent to identify areas of concern. Your auditor must be strong and supported enough to point out vulnerabilities without fear of retribution.

6. Written sanctions for non-compliance. The sanctions for non-compliance must be clear and widely publicized, and reviewed by all staff within 90 days of hire and, at minimum, annually.

7. Finally, your compliance plan needs to have a method to apply corrective action when violations are detected by monitoring and audit. Corrective actions include repayment of erroneously paid claims and/or disciplinary action.

Comment: If your compliance plan doesn't have a mechanism to perform corrective actions, a mistake could easily be redefined as fraud or abuse.

Keep it simple

It's important to keep your compliance plan simple. It needs to be a living document that all employees understand. If it sits on a shelf, it will do more harm than

(Continued on page 42)

Sample: Retina group compliance plan

Issued to all employees 1/1/2021
Review date:
A. **Written policies** are located on the practice shared drive in the folder labeled "Compliance." All staff members are sent a reminder to review the policies every January 1. Compliance policies:

a. Surgery policy: Review all surgery center claims for correct CPT and diagnosis prior to submission.
b. Modifier-25 policy and procedure: Run a Modifier-25 utilization report quarterly. Audit 10 percent of encounters billed with Modifier-25. Report findings to Practice Board.
c. Other areas of Office of Inspector General/ Centers for Medicare and Medicaid Services concern.

B. The practice compliance officer (CO) is Leslie Oversight. The CO reports directly to the Practice Board and is responsible for performing or assigning audits. The CO has an open-door policy and will investigate all compliance concerns within two business days. The CO will develop policies and procedures to address vulnerabilities and report complaints, investigation outcomes and remediation plans to the practice board.

Targeting headwaters of classical pathway

The IgG antibody fragment ANX007 aims to disrupt the cascade that leads to geographic atrophy at the initiating molecule.

By Richard Mark Kirkner, Editor

At last count, 10 candidates are in the investigative pipeline to treat geographic atrophy in dry, or non-neovascular, age-related macular degeneration. GA holds a strong allure for drug developers, the most obvious because no approved treatment currently exists and an estimated 5 million people worldwide have it.[1]

The mechanisms of action of these candidates are diverse: for example, an oral formulation of modified vitamin A (ALK-001, Alkeus Pharmaceuticals); a complement factor C5 inhibitor (Zimura, avacincaptad pegol, Iveric Bio); and an anti-sense oligonucleotide that inhibits CB gene expression (IONIS-F-LRx, Ionis Pharmaceuticals).

Another entry is ANX007 (Annexon Biosciences), an investigational monoclonal antibody antigen-binding fragment injected intravitreally designed to bind to C1q early in the complement pathway and inhibit the deleterious but enable the beneficial properties of downstream complement factors.

The ARCHER trial, a Phase II study evaluating ANX007 in 240 patients with GA commenced in February (NCT04656561). Completion is planned for December 2023.

Here, David R. Lally, MD, an investigator receiving grant support from Annexon, answers questions about ARCHER and ANX007. Dr. Lally is the director of the Retina Research Institute at New England Retina Consultants, an attending surgeon at Baystate Medical Center in Springfield and an assistant professor of surgery and ophthalmology at the University of Massachusetts Medical School-Baystate.

Q In your own words, please describe the mechanism of action of ANX007.

A ANX007 is an immunoglobulin G antibody fragment—a Fab fragment that's directed against C1q, the initiating molecule of the classical complement cascade. It's a humanized recombinant monoclonal antibody with a single heavy chain of the IgG1 isotype and a single light chain of the kappa isotype. It has a molecular weight of approximately 48 kDa. Early pharmacokinetic testing showed ANX007 was able to inhibit C1q for at least 29 days in the aqueous humor following a single intravitreal injection.

Previous genome-wide association studies identified a genetic link between polymorphisms in complement pathway proteins and AMD suggesting that complement pathway activity may play a role in AMD disease risk. C1q is involved in the initial step of the classical complement pathway. It also happens to be found accumulating in drusen and photoreceptor neuron synapses in the outer plexiform layer with aging.

We also know that C1q is produced by retinal microglia and macrophages and that it can activate the inflammasome, leading to local inflammation and potentially retinal atrophy. These observations support investigational therapies aimed to inhibit C1q to be studied in AMD.

Q What's novel about this treatment pathway compared to other candidates to treat GA?

A There are three distinct pathways through which complement can be activated: the classical; alternative; and lectin pathways. Each pathway follows a sequence of different reactions that result in the formation of a protease called C3 convertase. C3 convertase catalyzes the cleavage of C3 to C3a and C3b. From that point on, the complement system follows a single pathway culminating in the formation of C5a and C5b, resulting in activation of the inflammasome, formation of membrane attack complex, and ultimately cell death.

Apellis Pharmaceuticals' candidate, pegcetacoplan, or APL-2, is an inhibitor of complement factor C3 that's in late-stage inves-

ANX007 is an immunoglobulin G antibody fragment—a Fab fragment that's directed against C1q, the initiating molecule of the classical complement cascade.

tigation. By blocking C3, APL-2 attempts to inhibit all three pathways to maximize suppression of the entire complement system. Zimura targets inhibition of complement factor C5, which is downstream from C3, so it also attempts inhibit all three complement pathways.

ANX007, on the other hand, works upstream, inhibiting only the classical pathway, leaving the alternative and lectin pathways uninterrupted. The complement system plays an active role in the innate immune system, and it's unknown at this time whether blocking all three complement pathways or blocking one pathway without interrupting the other two will lead to differences in safety and efficacy outcomes.

Q What can you tell us about the Phase II ARCHER trial?

A This study is a Phase II, multicenter, randomized, parallel-group, double-masked trial investigating the efficacy, safety, and tolerability of ANX007 in the treatment of GA. Patients are randomized to one of four treatment groups: intravitreal injection of ANX00 7 5-mg monthly for 12 months; intravitreal injection of ANX00 7 5-mg every other month for 12 months; and sham treatment groups either monthly and every other month. Randomization is 2:2:1:1 with approximately 80 subjects in each ANX007 treatment group and 40 in each of the sham groups. ANX007 is injected at a volume of 0.1 mL, which is double that of standard anti-VEGF therapies.

The primary efficacy endpoint is the change from baseline to month 12 in the GA lesion area between each ANX007 arm and the pooled sham control arm.

Inclusion criteria requires a GA lesion area between 1.5 and 17.5 mm^2, and if the GA is multifocal, then at least one of the lesions must measure ≥1.25mm^2. The study allows the GA lesion to be located either foveally or non-foveally. A history of exudative choroidal neovascularization in the fellow eye is also permitted. Other key inclusion criteria include best-corrected visual acuity between 24 and 83 letters, or approximately 20/25 to 20/320 Snellen equivalent.

At month 12, the treatment period concludes and subjects are followed for an additional six months off-treatment.

Q What are the key secondary outcomes for ARCHER?

A Secondary outcome measures include the incidence and severity of ocular and systemic treatment-emergent adverse events, and change from baseline to month 12 in BCVA, low-luminance BCVA and low-luminance VA deficit. RS

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Is your 'new normal' compliant?

(Continued from page 40)

good. Your plan needs to support your efforts to avoid fraud and abuse, not be a bookshelf decoration. If an OIG representative visits your office, all employees should be able to say where the plan is located and confirm that they've reviewed it.

Although it's tempting to purchase a compliance plan, *caveat emptor*: An off-the-shelf plan may be too complicated, too expensive and blind to the real vulnerabilities for your practice. Will an off-the-shelf plan address Modifier-25 billing issues? Will it include retina-specific billing bundles as part of its auditing recommendations? Probably not, unless you purchase an ophthalmology-specific plan. You also want to be sure the template includes customer support to answer questions and help guide you as you write your plan.

Without a template, what are your options? You could use the seven core elements listed previously and expanded in the previously cited footnotes, and develop your plan. Your plan might look something like the sample in the box on page 40.

The simpler your plan, the easier it will be to get started. Over time, your plan will expand in some areas as your compliance officer identifies areas of risk. Other policies may be retired as risks recede. That's what a living document is supposed to do: evolve with your practice to keep your activities compliant.

Bottom line

Compliance may sound awful at first blush, but for the engaged compliance officer, it's an interesting and evolving challenge. Finding the right compliance officer to lead your program, even if the task falls to you, with enthusiasm, an open and welcoming attitude and a strong attention to auditing details can make all the difference in your success. It's time to reinvent your practice with an eye toward compliance. RS

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LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

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

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
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A Member of the Roche Group
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South San Francisco, CA
94080-4990

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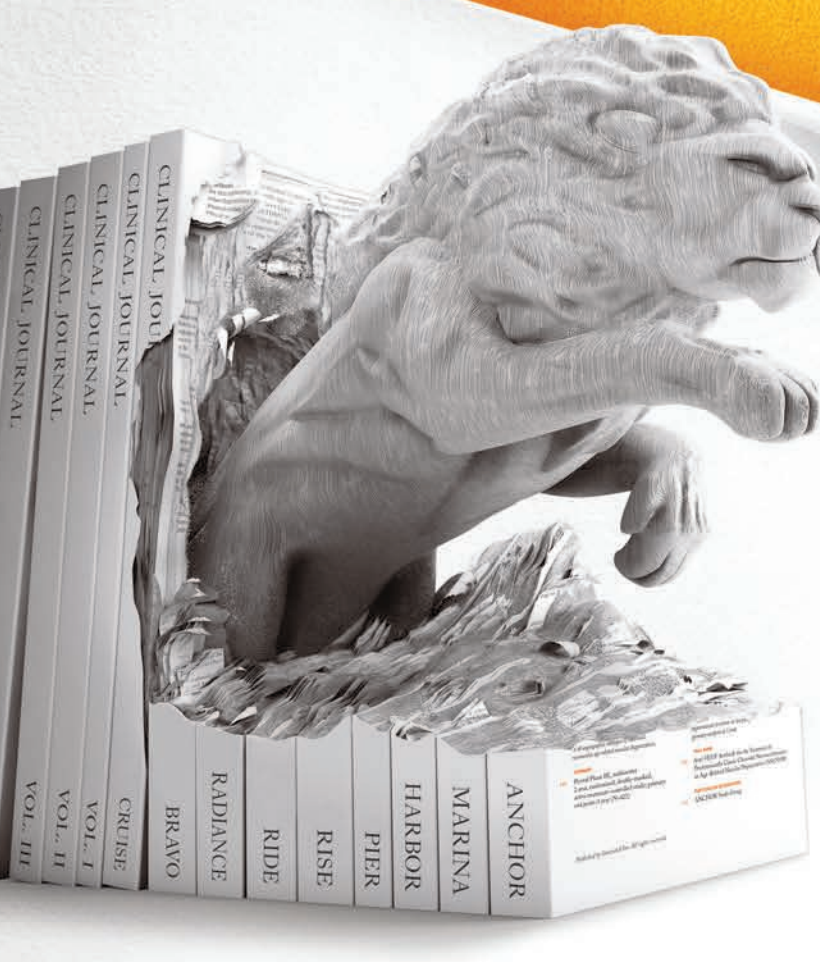
Revision Date: M-US-00002319(v1.0) 2019



LUCENTIS®
RANIBIZUMAB INJECTION

STRENGTH IN VISION

LUCENTIS has been extensively studied and FDA approved in 5 retinal indications.

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation
- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection with LUCENTIS
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

Please see Brief Summary of LUCENTIS full Prescribing Information on following page.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Randomized, double-masked clinical trials conducted for the 5 LUCENTIS indications included the following: **wAMD:** *MARINA, ANCHOR, PIER, HARBOR*. **DR and DME:** *RISE, RIDE*. **mCNV:** *RADIANCE*. **RVO:** *BRAVO, CRUISE*.[1-10]

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