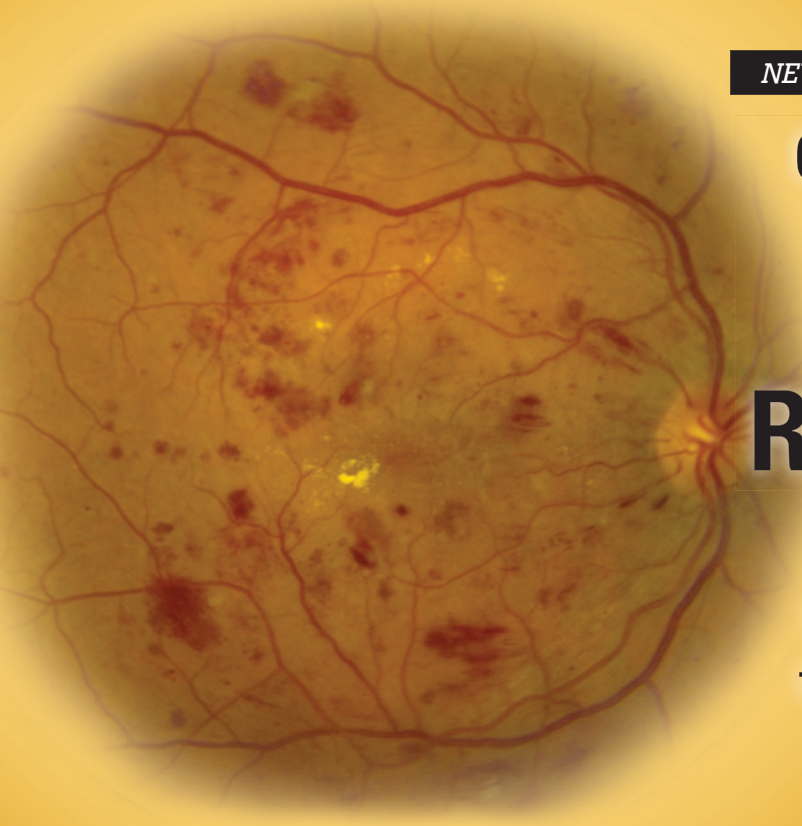
A PUBLICATION BY REVIEW of Ophthalmology

RETINA SPECIALIST

VOL. 6, NO.3 • MAY/JUNE 2020



NEW INSIGHTS FOR DIABETIC EYE DISEASE

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19 Campus Blvd., Suite 101
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Telephone (610) 492-1000
Fax (610) 492-1039

Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

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EDITORIAL

By Charles C. Wykoff, MD, PhD

Quarantine

The term derives from Italian, *quaranta giorni*, or 40 days. As the plague ravaged European cities in the 14th century, the practice was put into place to protect coastal cities. Ships arriving in Venice from ports deemed to be infected were required to remain at anchor for 40 days before docking.

In the United States, authority for instituting a quarantine was bestowed on the Centers for Disease Control and Prevention in 1967, and while this power wasn't used in this pandemic, by mid-March 2020, we had essentially entered our first nationwide quarantine. Nearly everything about our daily lives changed, with three apparent overarching themes.

• ***Fear.*** To date, fear has been the strongest and most consistent emotion. Most of our patients are in high-risk categories. Despite any office-level protocols to minimize risk, they and their families are, rightfully, scared.

Doctors and support staff are also rightfully anxious for a host of reasons. It's stressful to consider that every patient may have the virus and that if we lapse in respecting contact precautions, we may be the unwitting agent who infects a host of patients, potentially becoming the equivalent of the next super spreader. Simultaneously, balancing home-schooling for many doctors and staff adds another unprecedented dynamic of tension.

• ***Uncertainty.*** There has been broad geographic variability in the impact of COVID-19 on retina practices. Some practices have shuttered, furloughing or laying off large proportions of staff with an unclear trajectory for restarting. Most have experienced dramatic reductions in patient volumes while continuing to care for patients who need ongoing intravitreal injections and selected surgeries.

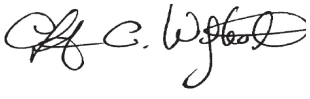
Perspectives on appropriate use of personal protective equipment, now ingrained in our lexicon as *PPE*, have been notably contentious, exacerbated by the lack of adequate supplies, incomplete data to drive local institutional policies, and shortage of accurate and efficient viral testing.

• ***Adaptation.*** Retina was largely defined by in-person meetings, lots of them. These have now essentially disappeared for the foreseeable future, and we've been immersed in a virtual word. As we navigate the likes of Zoom and GoToMeeting, we've learned the intricacies of this ecosystem, including virtual backgrounds, camera placement and chat functions. More heroically, in some of the hardest hit regions, ophthalmologists have transitioned to serving in ERs or general medical floors.

As of early May, some regions started to relax restrictions to reverse the economic devastation. Undercurrents of fear and uncertainty that have defined our darkest days are giving way to hope and a brighter outlook.

The resilience and courage we've witnessed in our colleagues from Seattle to New York to Louisiana inspire us to continue to care for our patients in the midst of this new and evolving normal of paranoia and contagion.

Our world is changed. In these times, and hopefully more so in the times to come, we must look out for, lend a hand to and encourage each other. Stay well.



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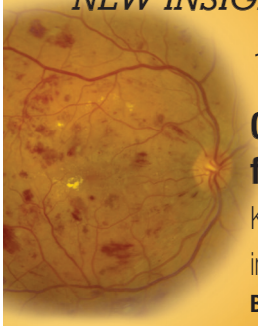
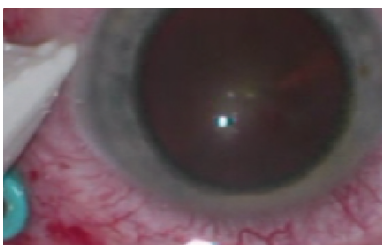
FEATURES

NEW INSIGHTS FOR DIABETIC EYE DISEASE



DEPARTMENTS



More lessons learned in a COVID-19 hotspot

Before the COVID-19 pandemic resulted in stay-at-home orders in the United States, a retina specialist in Hong Kong and colleagues reported on steps they'd taken to improve infection control measures in their ophthalmology clinic during the coronavirus outbreak there. The article, published online in *Graefe's Archive for Clinical and Experimental Ophthalmology*,[1] was widely circulated in the United States. For almost two months, it led MDLinx's list of top-read articles in ophthalmology.

Senior author Kenneth K.W.Li, MCBhB, FRCS, agreed to answer questions from *Retina Specialist* about his team's experience during the pandemic and lessons for U.S. colleagues. Dr. Li is chief of ophthalmology at United Christian Hospital/Tseung Kwan O Hospital in the Kowloon East Cluster Hospital Authority.

Q As a retina specialist, how have you fared communicating with patients who need regular intravitreal injections? Have they kept their appointments?

A We are extremely fortunate that infection and deaths from COVID-19 in Hong Kong have been kept low and we are not in a complete lockdown. As a result, we are still continuing our regular intravitreal injections. As most of our patients understand any delay of intravitreal injections can have a detrimental effect on their vision, we are not seeing a substantial reduction in attendance.

Kenneth K.W.Li, MCBhB, FRCS, with the puppy guide dog Valter. ***(Photo by Rolan Chu)***

However, recent surveys by the American Society of Retinal Specialists[2] showed a lack of consensus among its members on the management of patients requiring intravitreal treatment in the current pandemic. The Vision Academy recently published a paper to provide guidance on intravitreal injections to the vitreoretinal community.[3] It suggested a three-tier approach:

- prioritize patients with the greatest needs;
- adjust injection intervals for existing cases; and
- protection for both patients and health-care workers.

These general principles are more relevant than established college guidelines, as there is much variation among different countries in the state of the COVID outbreak, local regulations and service capacities. Nevertheless, patients should be provided with clear instructions on the situation and arrangements.

Q What insights have you gained since publication of your paper that would aid other physicians?

A Over the past few months, the global ophthalmic communities have been focusing on stepping up infection-control measures. However, it's important not to overlook the psychological and mental wellness of our colleagues, especially because the current pandemic may last longer than we expected.

Health-care workers have been facing immense stress from increased workloads, infection risks, physical stress, psychological stress or even burnout. Independent practitioners may worry about the possibility of financial turmoil due to suspension of clinical practices. With prolonged lockdown situations in many countries, many health-care workers are also juggling work and family commitments. Management should hold regular staff meetings to understand and address their concerns.

In our department, we hold weekly situation update meetings with our staff. Since March, we implemented flexible leave arrangements for our colleagues. We allow staff to cancel their annual leave as their original travel plans can no longer be realized, due to either travel restrictions or their worry about infection risks associated with traveling. On the other hand, staff with small children may

IN BRIEF

Adverum Biotechnologies has dosed the first patient in cohort 4 of the ongoing OPTIC Phase I clinical trial for ADVM-022, a gene therapy candidate for the treatment of wet age-related macular degeneration. Nine patients in cohort 4 are receiving a single intravitreal injection of ADVM-022 at a dose of 6 x 10^{11} vg/eye (same as cohort 1) plus a steroid eye drop prophylaxis for six weeks (same as cohort 3).

The Food and Drug Administration granted **Iveric bio** Fast Track designation for **Zimura** (avacincaptad pegol), a novel complement factor 5 inhibitor for the treatment of geographic atrophy secondary to dry age-related macular degeneration, Iveric announced.

Icare USA has completed its merger with ophthalmic imaging company **CenterVue** after the Finnish Revenio Group Corp. acquired CenterVue. The merged company will be known as Icare USA.

want to take time off to look after family, and we allow them to take annual leave, even with a short notice of one week. Of course, they understand the bottom line: that there must be adequate staffing for our clinical service.

This initiative is well received by our staff. It's important to let our staff know that we're all in the same boat and eager to help each other.

Q Are you back to using non-contact tonometry yet?

A We haven't resumed the use of NCT. Because of the concern of NCT generating microaerosol, we are still cautious about its use. I understand investigators worldwide are already studying this area and more evidence should be available soon.

We have preemptively adopted three measures to reduce the transmission risk. First, to limit intraocular pressure measurement only to indicated cases, including recent postoperative cases, those on anti-glaucoma and steroid eye drops, and first-visit cases. Second, to cease all NCT use in our triage stations and replace it with iCare tonometry. And third, to perform all Goldmann tonometry with disposable applanation tips.[4]

Q How have you fared with retina surgery that requires general anesthesia?

A Both the British and Eire Association of Vitreoretinal Surgery and ASRS recently issued recommendations on the use of eye protection and FFP3/N95 respirators for pars plana vitrectomy.[5] This is likely due to the high-speed nature of PPV and its potential aerosol generation. This has sparked intense discussion in the vitreoretinal community. An even greater concern is phacoemulsification with its much higher frequency than PPV. More study is warranted in the aerosol-generating nature of both PPV and phacoemulsificaiton.

We recently published a risk-stratification protocol for emergency surgery that our hospital has had in place since February.[6] All patients are screened by the questionnaire on fever, travel, occupation, contact and clustering, and only high-risk cases undergo the COVID-19 rapid test.[1] COVID status will determine the level of precautions and the need of negative-pressure operating facilities. Our preliminary experience has shown reduction in both the consumption of personal protective equipment and utilization of negative-pressure operating facilities. RS

REFERENCES

1. Lai TH, Tang EW, Chau SK, Fung KS, KK Li. Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong. Graefes Arch Clin Exp Ophthalmol. Published online March 3, 2020.
2. Third COVID-19 member survey. American Society of Retina Specialist. https://www.asrs.org/clinical/clinical-updates/3997/results-are-in-3rd-covid-19-member-survey. Updated April 29, 2020. Accessed May 4, 2020.
3. Korobelnik JF, Loewenstein A, Eldem B, et al. Guidance for anti-VEGF intravitreal injections during the COVID-19 pandemic. Graefes Arch Clin Exp Ophthalmol. Published online April 23, 2020.
4. Ng VW, Tang GH, Lai TH, Tang EW, Li KK. Intraocular pressure measurement during COVID pandemic. Indian J Ophthalmol. 2020;68:950-951.
5. Recommendations for conducting vitreoretinal surgery during the COVID-19 pandemic. ASRS. https://files.constantcontact.com/98b7aceb001/c27fdd27-223d-45bc-90f3-031cd4f4cec0.pdf Accessed May 4, 2020.
6. Wong DH, Tang EW, Njo A, Chu CK, Chau SK, Lim HS, Fung KS, Li KK. Risk stratification protocol to reduce consumption of person protective equipment for emergency surgeries during COVID-19 pandemic. Hong Kong Med J. In Press.

Table omitted agents

A table in the article "Gene therapy and editing for the retina: A primer" (page 22, March/April 2020) listing clinical trials in inherited retinal disease omitted three agents:

- AAV-RGPR for X-linked retinitis pigmentosa;
- AAV-CNGB3 to restore cone function in achromatopsia caused by CNGB3 gene mutations; and
- AAV-CNGA3 to restore cone function in achromatopsia caused by CNGA3 gene mutations.

Developer of the therapies is Janssen/MeiraGTx.
The table has been updated on www.retina-specialist.com.
Retina Specialist regrets the omission.

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BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

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SENIOR CIRCULATION MANAGER
JARED SONNERS
(973) 206-8091 jsonners@mdedge.com

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Flashing, blind spots and retinal dots

Multimodal imaging helps clinch the diagnosis.

By Luv G. Patel, MD and Jason Hsu, MD


Luv G. Patel, MD


Jason Hsu, MD

A 39-year-old woman presented with a two-week history of photopsias and a subjective temporal scotoma in her right eye. She denied any eye pain. Her medical history was unremarkable. Her ocular history was notable for -3.5 D spherical myopia OU. She denied any additional symptoms on a review of systems or relevant family history.

Findings upon presentation

The patient appeared generally healthy. Snellen visual acuity with correction was 20/40 OD and 20/20 OS. Intraocular pressures were 13 mmHg OD and 16 mmHg OS. Pupillary examination demonstrated round and reactive pupils without a relative afferent pupillary defect. Although a subjective scotoma had been reported, the patient demonstrated full confrontational visual fields. Slit-lamp examination was unremarkable in both eyes without evidence of anterior chamber cell or flare.

Posterior examination of the right eye revealed clear media without vitritis. We also noted punctate multifocal white-yellow retinal lesions around the optic nerve, most prominent in the nasal macula and nasal midperiphery (*Figure 1A*). We also saw a single area of scarring in the inferotemporal peripapillary region. Posterior examination of the left eye was unremarkable.

What imaging revealed

Fundus autofluorescence of the right eye revealed punctate hypoautofluorescence over the multifocal yellow-white lesions seen on funduscopy (*Figure 1C*). A ring of hyperautofluorescence surrounded the punctate areas of hypoautofluorescence, coalescing into a patchy ring of hypoautofluorescence centered around the optic disc. The temporal macula had additional faint amorphous areas of hyperautofluorescence without central hypoautofluorescence distinct from the multifocal lesions seen on funduscopy.

Indocyanine green angiography of the right eye demonstrated multifocal areas of early hypocyanescence (*Figure 2A*) that remained hypocyanescent into the late phase. While many of them corresponded to the lesions seen on funduscopy, there were additional foci of hypocyanescence. The areas of hypocyanescence were also larger than the clinical lesions. Fluorescein angiography

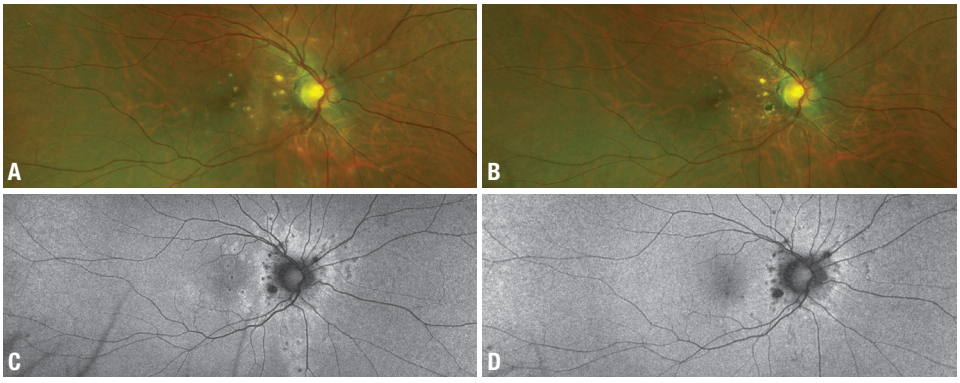

Figure 1. Color image at presentation (A) shows posterior-pole multifocal yellow-white lesions with a single focal scar inferotemporal to the disc in the peripapillary region. Three months later (B), the lesions have regressed and consolidated. Baseline fundus autofluorescence (C) shows numerous foci of hypoautofluorescence surrounded by hyperautofluorescence. Three months later (D), some hypoautofluorescent areas persist, but the surrounding hyperautofluorescence has resolved.

Bios
Drs. Patel and Hsu are with Mid-Atlantic Retina / Retina Service, Wills Eye Hospital, Philadelphia.

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

showed early hyperfluorescence (*Figure 2C*) of the punctate lesions with staining in the late phase (*Figure 2D*).

Optical coherence tomography of the right eye demonstrated deposits of moderate hyperreflectivity at the level of the inner choroid with elevation of the retinal pigment epithelium and subsequent disruption of the photoreceptor layer in the outer retina (*Figure 3A, page 10*). The single area of scarring revealed disruption of the RPE with atrophy of the overlying outer retinal layers (*Figure 3B, page 10*).

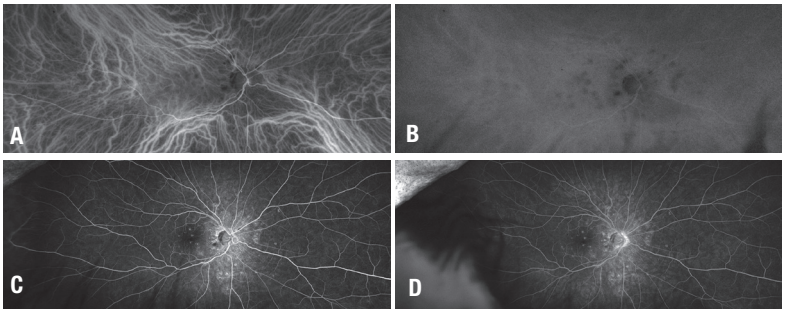

Figure 2. Early phase indocyanine green angiography (A) shows hypocyanescence corresponding to the white-yellow lesions on fundoscopy. Late-phase ICGA (B) shows persistent hypocyanescence corresponding to the white-yellow lesions on fundoscopy. The region of hypocyanescence is larger than yellow-white lesions and numerous areas of hypocyanescence that don't correlate to funduscopic lesions are visible. Early venous-phase fluorescein angiography (C) shows hyperfluorescence of the yellow-white lesions. Late-phase FA (D) shows persistent hyperfluorescence consistent with staining without any leakage.

Testing and diagnosis

The differential diagnosis of multifocal white dots is broad, and includes inflammatory and infectious etiologies. Possible inflammatory etiologies include:

- punctate inner choroidopathy (PIC);
- presumed ocular histoplasmosis syndrome;
- multifocal choroiditis;
- multiple evanescent white dot syndrome; and
- sarcoidosis.

We also considered possible infectious etiologies, including syphilis and tuberculosis, although these aren't typically unilateral. Serological testing for syphilis and tuberculosis, and chest X-ray were normal. Based on the clinical presentation and classical multimodal imaging described above, we made a clinical diagnosis of PIC.

Disease presentation

Robert Watzke, MD, and colleagues first described PIC in 1984 with a cohort of 10 young myopic women.[1] They reported yellow-gray lesions at the level of the inner choroid and RPE. Subsequent series reporting larger cohorts characterized the lesions as 100 to 300 µm in size with a predilection for the posterior pole in a generally random pattern.[2,3] These characteristic lesions and absence of both iritis and vitritis can differentiate PIC from other white-dot syndromes.

In one series, the most common symptoms were scotoma, blurred vision, photopsia, floaters, photophobia and metamorphopsia.[4] Visual acuity at presentation is variable; however, a majority of patients in retrospective studies tended to present at 20/50 or better.[1–3,5] The disease can be bilateral or unilateral. The literature describes a variable rate of the former.[1,3,6]

The natural disease course is variable. In rare cases the lesions self-resolve. More commonly, the lesions progress to chorioretinal scarring with a "punched-out" appearance. The scars often represent areas of permanent scotomas. If the lesions involve the fovea, they can lead to a loss of central acuity. A substantial risk of choroidal neovascularization is associated with the lesions, with rates reported at 20 to 70 percent.[1,3–5]

The diagnosis is clinical

Multimodal imaging is especially useful in aiding the diagnosis and determining the extent of the disease. OCT imaging can often confirm lesion depth at the level of the inner choroid and RPE. Breakage of the RPE is an OCT feature that often distinguishes lesions associated with permanent scarring.[7]

Indocyanine green angiography identifies areas of hypoperfusion at the level of the choriocapillaris and highlights lesions that are subclinical on funduscopy.[7,8] Fluorescein angiography is often useful in identifying

and confirming the presence of CNV.

Fundus autofluorescence is particularly helpful for assessing disease activity and treatment response. Areas of hyperautofluorescence correlate with areas of active inflammatory disease at the level of the RPE. Regression in hyperautofluorescence signifies amelioration of active inflammation either from the natural course or treatment.[9]

Treatment

Given the risk of permanent vision loss from both the disease course and associated CNV, most retina specialists and patients elect immunosuppression once the diagnosis is established. Corticosteroids are often the first choice in treatment; both systemic and intravitreal steroids have been used. The benefit of either form is unclear based on retrospective studies, although there is suspected bias because advanced cases are more likely to receive treatment.[3,4]

With systemic steroids, a prednisone taper is often initiated. Steroid-sparing agents are considered if the disease relapses and the patient can't be safely tapered off systemic steroids.[10] Treatment duration is often patient-specific depending on the risks vs. benefits of long-term immunosuppression. Although controversial, some providers will initiate long-term, steroid-sparing agents on presentation.

If CNV develops, anti-VEGF agents are the first-line treatment of choice, although photodynamic therapy has been reported as an alternative. Development of CNV doesn't necessarily signify active inflammatory disease.

In this case, we initiated oral prednisone 60 mg per day with a slow taper. Two months after presentation, the patient's visual acuity improved to 20/20, and the photopsias and subjective scotoma had resolved.

On fundus examination, the yellow-white punctate lesions had shrunken and consolidated with sharp margins (*Figure 1B, page 8*). Fundus autofluorescence was notable for persistent foci of hypoautofluorescence. The rings of hyperautofluorescence, however, had resolved (*Figure 1D, page 8*).

Bottom line

PIC is characterized by multifocal inflammation of the inner choroid and RPE without the associated vitritis that often occurs in young, myopic females. Lesions are initially elevations at the RPE level, but areas of chronic inflammation can lead to permanent scarring with a "punched-out" appearance.

The diagnosis is clinical and multimodal imaging plays a key role in confirming and identifying areas of subclinical inflammation. Additionally, fluorescein angiography can be helpful in detecting CNV.

Treatment of the inflammatory process is often with local or systemic immunosuppression. Anti-VEGF treatment is indicated for CNV. Multimodal imaging is paramount to evaluate disease activity as well as treatment response.

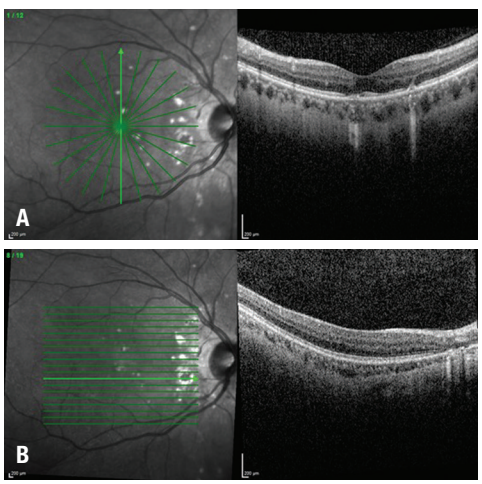

Figure 3. Spectral domain optical coherence tomography at presentation (A) demonstrates hyperreflective lesions at the level of the inner choroid and retinal pigment epithelium with corresponding areas of photoreceptor disruption. At follow-up (B), SD-OCT shows persistent peripapillary scarring with loss of outer retinal layers.

REFERENCES

1. Watzke RC, Packer AJ, Folk JC, Benson We, Burgess D, Ober RR. Punctate inner choroidopathy. Am J Ophthalmol. 1984;98:572–584.
2. Kedhar SR, Thorne JE, Wittenberg S, Dunn JP, Jabs DA. Multifocal choroiditis with panuveitis and punctate inner choroidopathy: comparison of clinical characteristics at presentation. Retina. 2007; 27:1174–1179.
3. Essex RW, Wong J, Fraser-Bell S, et al. Punctate inner choroidopathy: clinical features and outcomes. Arch Ophthalmol. 2010; 128:982–987.
4. Gerstenblith AT, Torne JE, Sobrin L, et al. Punctate inner choroidopathy: a survey analysis of 77 persons. Ophthalmology. 2007;114:1201–1204.
5. Brown J, Folk JC, Reddy CV, Kimura AE. Visual prognosis of multifocal choroiditis, punctate inner choroidopathy, and the diffuse subretinal fibrosis syndrome. Ophthalmology. 1996;103:1100–1105.
6. Zhang X, Wen F, Zuo C, Li M, et al. Clinical features of punctate inner choroidopathy in Chinese patients. Retina. 2011;31:1680–1691.
7. Zhang X, Zuo C, Li M, Chen H, Huang Sm Wen F. Spectral-domain optical coherence tomographic findings at each stage of punctate inner choroidopathy. Ophthalmology. 2013;120:2678–2683.
8. Tiffin PAm Maini R, Roxburgh ST, Ellingford A. Indocyanine green angiography in a case of punctate inner choroidopathy. Br J Ophthalmol. 1996;80:90–91.
9. Li M, Zhang Xm Wen F. The fundus autofluorescence spectrum of punctate inner choroidopathy. J Ophthalmol. Published online July 22, 2015.
10. Turkcuoglu P, Chang PY, Rentiya ZS, et al. Mycophenolate mofetil and fundus autofluorescence in the management of recurrent punctate inner choroidopathy. Ocul Immunol Inflamm. 2011;19:286–292.

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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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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

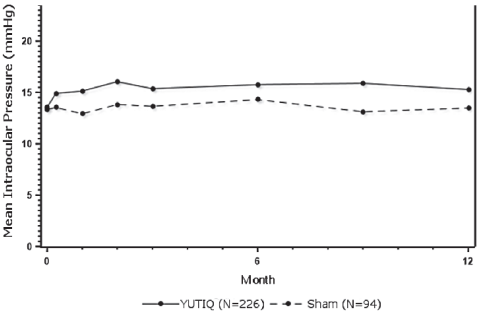
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

Managing TRC in posterior uveitis

Guidance for detecting and managing toxoplasmosis retinochoroiditis.
By Priya Janardhana, MD, and Soraiya Thura, MD

Ocular toxoplasmosis, the most common cause of posterior uveitis,[1-3] is a manifestation of infection from the intracellular protozoan *Toxoplasma gondii*. Infection is often acquired through ingestion of contaminated water or food. Transplacental transmission infecting the fetus has also been reported.[1-5]

Classical clinical presentation

The usual presenting symptoms of ocular toxoplasmosis are floaters and blurred vision. Clinical findings are actually the result of inflammation due to reactivation of the infection that occurred *in utero* or after birth. The retina is the most common ocular site for infection, but the underlying choroid can become inflamed secondarily, leading to retinochoroiditis.

The classic presentation of toxoplasmosis retinochoroiditis (TRC) is a fluffy white nidus of retinitis often adjacent to a pigmented chorioretinal scar, with overlying vitritis, producing the classic "headlight in the fog" finding.[1,5] Lesion size and thickness can dictate the amount of vitreous haze and cell.[6]

Vision loss can be due to a macular chorioretinal scar, optic-nerve involvement or severe vitreous inflammation adjacent the chorioretinal lesions. About one-third of cases can include retinal vasculitis, usually arteriolitis *(Figure 1)*.[7] In addition to posterior involvement, patients with TRC can have secondary iridocyclitis with granulomatous or stellate keratic precipitates. Secondary inflammatory ocular hypertension can develop in 10 to 15 percent of cases.[1,5]

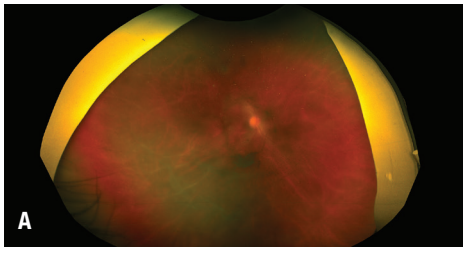
TRC may also present as neuroretinitis, punctate outer retinal toxoplasmosis, occlusive retinal vasculitis or infarction, papillitis, and retinal detachments. Though not common, optic-nerve involvement may produce severe visual field defects (*Figure 2, page 14*). In these unique cases, specialized lab testing can be very helpful.[8,9]

Diagnostic testing

The diagnosis of TRC is usually made by recognizing its distinctive clinical findings on funduscopy. In atypical cases, further lab testing with serum anti-toxoplasma antibodies, both IgM and IgG, may be needed.[4,8] Toxoplasma serologic testing, when negative, can be useful to exclude toxoplasmosis as a cause of posterior uveitis; IgG has high prevalence of seropositivity in most communities, and IgM has a variable rate of decline after acutely acquired infection.[8,10,11] In challenging cases, ocular fluid testing with protein catabolic rate (PCR) of aqueous or vitreous samples can also be done.[1,2]

Imaging as a tool

Spectral-domain optical coherence tomography imaging is important in the diagnosis and management of TRC, with



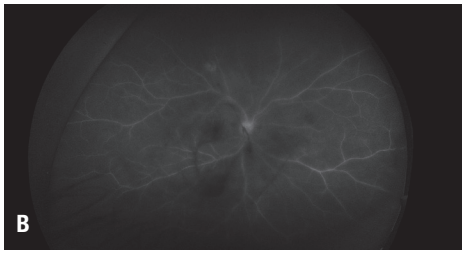


Figure 1. Color image (A) of toxoplasmosis chorioretinitis with associated retinal vasculitis. Late-phase fluorescein angiography (B) displays perivascular leakage, confirming retinal vasculitis associated with TRC. (*Photos courtesy Jessica Peterson and Katlyn Champagne, UMass Memorial Eye Center, Worcester*)


Priya Janardhana, MD


Soraiya Thura, MD


Akshay S. Thomas, MD, MS

Bio

Dr. Janardhana is director of the uveitis service and assistant professor of ophthalmology at the University of Massachusetts Medical School, Worcester.

Dr. Thura is an ophthalmology resident at the University of Massachusetts Medical School, Worcester.

Dr. Thomas is an associate in vitreoretinal surgery and uveitis at Tennessee Retina, with offices in central Tennessee and southern Kentucky.

DISCLOSURES: Drs. Janardhana, Thura and Thomas have no relevant financial relationships to disclose.

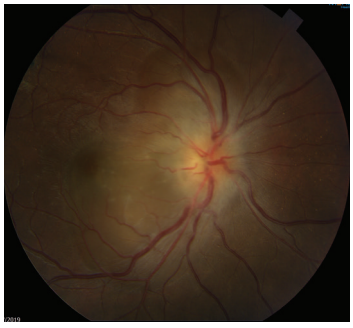


Figure 2. Magnified view of toxoplasmosis chorioretinitis and optic nerve edema.

changes observed based on the disease stage.[9,11,12] Neurosensory retina thickening and disruption can be seen acutely. The epiretinal membrane may appear overactive or chronically scarred lesions (*Figure 3*).[1] Collectively, fundus photography, OCT and fluorescein angiography help to document inflammation and follow complications such as macular edema, vascular occlusions and choroidal neovascularization.[12]

Treatment options

The role of systemic antibiotics for ocular toxoplasmosis has been debated extensively. Ultimately, each patient's safety profile and location of the TRC lesion should drive the choice. TRC is self-limiting in most immunocompetent patients with a course of four to eight weeks; the risk of potential toxicity from antiparasitic medications may outweigh the benefit.[7,11] Patients with small extramacular lesions that aren't vision-threatening don't require treatment.

However, patients who are pregnant or immunocompromised, or have vision-threatening lesions need immediate treatment (*Table*). There's also some thought that treating even extramacular lesions may reduce the risk of secondary retinal detachment.

The classic "triple-drug therapy" has long been the combination of oral pyrimethamine and sulfadiazine with systemic corticosteroids. Unfortunately, pyrimethamine can produce bone-marrow suppression in approximately 25 percent of patients as well as thrombocytopenia, rashes and fever.[7] Folinic acid can limit these suppressive effects, but weekly monitoring of leukocyte and platelet counts are essential.

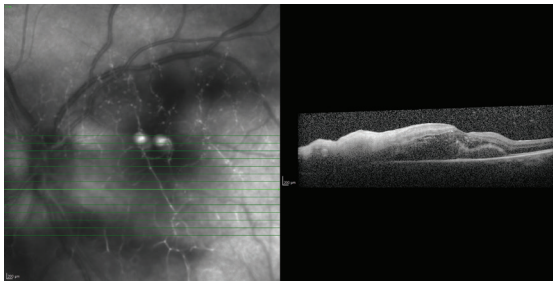


Figure 3. Macula optical coherence tomography through an area of toxoplasmosis chorioretinitis shows full-thickness retinal involvement with underlying choroidal thickening.

Trimethoprim-sulfamethoxazole (Bactrim) has an overall more favorable safety profile than pyrimethamine and has been shown to be as effective in treating TRC.[13] However, skin rashes occur in more than 10 percent of patients, as do rare severe hypersensitivity reactions such as Stevens-Johnson syndrome.[1,7,10,11,14] Level I evidence has also shown that intermittent Bactrim (one tablet every three days) can be used as long-term prophylaxis against TRC recurrence.

The pyrimethamine/sulfadiazine and trimethoprim-sulfamethoxazole combinations are contraindicated in patients with sulfa-drug allergies. Alternative systemic treatments with equally successful outcomes are clindamycin, azithromycin and atovaquone.[7] Most of the drugs target the tachyzoites primarily, but don't eradicate the encysted forms. Atovaquone is effective in killing both the tachyzoites and the cyst forms of toxoplasmosis, but requires close liver-function monitoring.[15]

Role of systemic corticosteroids

Systemic corticosteroids (1 mg/kg) should be started 48 hours after initiating TRC antimicrobial therapy. They're especially helpful in recovery in patients with significant vitritis, associated optic edema and retinal vasculitis, and can help reduce inflammation surrounding the chorioretinal lesion. Corticosteroids are typically tapered slowly over four to six weeks and stopped before the antimicrobial therapy.

Intravitreal therapy

In patients with contraindications or who don't respond to systemic therapy, a combination of intravitreal clindamycin (1 mg/0.1 mL) and dexamethasone (0.4 mg/0.1 mL) is a safe option, especially in cases with macular or juxtapapillary involvement (*Figure 4*). A few clinical trials have reported no difference in visual acuity, lesion size, resolution of inflammation, or recurrence between those treated with intravitreal clindamycin/dexamethasone or classic therapy of pyri-

Systemic treatments for toxoplasmosis chorioretinitis

Medication*	Dosage	Safe During Pregnancy
Pyrimethamine/ sulfadiazine with systemic corticosteroids (given with folinic acid)	Pyrimethamine	
	Loading dose: 50 to 100 mg p.o./day; Treatment dose: 25 to 50 mg p.o./day	Category C: Avoid in first and last trimester
	Sulfadiazine	
	<60 kg: 1,000 mg p.o. q6h >60 kg: 1,500 mg p.o. q6h	Category C: Avoid in first and last trimester
	Prednisone	
	1mg po/kg/day with taper	Category D: Can cause cleft lip or palate, premature delivery, low birth weight
Trimethoprim-sulfamethoxazole (Bactrim)	160/800 mg (Bactrim DS) p.o. b.i.d	Category C: Avoid if possible, especially in first trimester and last month of pregnancy
Clindamycin	300 mg p.o. q.i.d.	Category B: Safe
Azithromycin	250 mg p.o. daily	Category B: Safe
Atovaquone	750 mg p.o. q.i.d.	Category C: Controversial; may use if other medications contraindicated

Key: * All medications given over a course of six weeks.

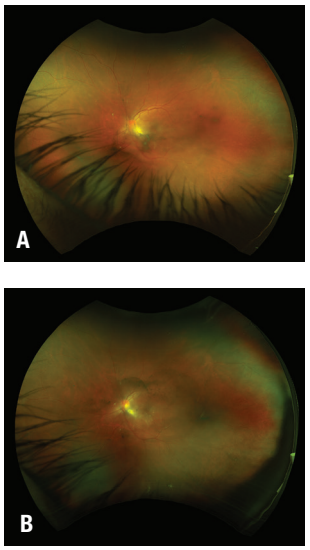


Figure 4. Color image (A) shows toxoplasmosis chorioretinitis with macular and juxtapapillary involvement. Twelve days after intravitreal clindamycin/dexamethasone (B), the focal area of retinal necrosis and inflammation due to TRC is decreased.

methamine, sulfadiazine and oral prednisone. Intravitreal clindamycin/dexamethasone often requires more than one dose every one to two weeks.[7,16] Adding systemic therapy to pyrimethamine, sulfadiazine and oral prednisone with intravitreal clindamycin/dexamethasone hasn't shown any additional benefit.[17] Hence, intravitreal clindamycin/dexamethasone is a reasonable first-line treatment.

Bottom line

The choice of treatment for TRC depends on the patient's immune status, drug contraindications, disease location and severity, and potential drug toxicities. RS

REFERENCES

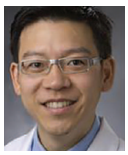
1. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Exp Ophthalmol. 2013;41:95-108.
2. Barb SM, Patel AV, Young LH. Toxoplasmic retinitis. Int Ophthalmol Clin. 2015;55:137-145.
3. Maenz M, Schlüter D, Liesenfeld O, Schares G, U Gross U, Pleyer U. Ocular toxoplasmosis past, present and new aspects of an old disease. Prog Retinal Eye Res. 2014;39:77-106.
4. Petersen E, Kijlstra A, Stanford M. Epidemiology of ocular toxoplasmosis. Ocular Immunol Inflamm. 2012;20:68-75.
5. Bosch-Driessen LE, Berendschot TT, Ongkosuwito JW, Rothova A. Ocular toxoplasmosis: clinical features and prognosis of 154 patients. Ophthalmology. 2002;109:869-878.
6. Dodds EM, Holland GN, Stanford MR, et al. Intraocular inflammation associated with ocular toxoplasmosis: relationships at initial examination. Am J Ophthalmol. 2008;146:856-865.
7. Harrrel M, Carvounis PE. Current treatment of toxoplasma retinochoroiditis: an evidence-based review. J Ophthalmol. Published online August 13, 2014.
8. Garweg JG, de Groot-Mijnes JDF, Montoya JG. Diagnostic approach to ocular toxoplasmosis. Ocular Immuno Inflamm. 2011;19:255-261.
9. Burke S, Fine H, Albini T. Toxoplasmosis retinitis masquerading as acute retinal necrosis. Ophthalmic Surg Lasers Imaging Retina. 2016;47:895-899.
10. Tabbara KF. Ocular toxoplasmosis: Toxoplasmic retinochoroiditis. Int Ophthalmol Clin. 1995;35:15-29.
11. Ozgonul C, Besirli CG. Recent developments in the diagnosis and treatment of ocular toxoplasmosis. Ophthalmic Res. 2017;57:1-12.
12. Brandão-de-Resende B, Balasundaram MB, Narain S, Mahendradas P, Vasconcelos-Santos DV. Multimodal Imaging in Ocular Toxoplasmosis. Ocular Immunol Inflamm. 2020;11:1-9.
13. Soheilian M, Sadoughi MM, Ghajarnia M, et al. Prospective randomized trial of trimethoprim/sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis. Ophthalmology. 2005;112:1876-1882.
14. Kim SJ, Scott IU, Brown GC, et al. Interventions for toxoplasma retinochoroiditis: a report by the American Academy of Ophthalmology. Ophthalmology. 2013;120:371-378.
15. Pearson PA, Piracha AR, Sen HA, Jaffe GJ. Atovaquone for the treatment of toxoplasma retinochoroiditis in immunocompetent patients. Ophthalmology. 1999; 106:148-53.
16. Sobrin L, Kump LI, Foster CS. Intravitreal clindamycin for toxoplasmic retinochoroiditis. Retina. 2007;27:952-957.
17. Bori A, Mahrous A, Al-Aswad MA, et al. Intravitreal clindamycin and dexamethasone combined with systemic oral antitoxoplasma therapy versus intravitreal therapy alone in the management of toxoplasma retinochoroiditis: A retrospective study. J Ophthalmol. Published online February 12, 2018.

Fixing a malpositioned infusion cannula

Setting it right during pars plana vitrectomy can avoid serious complications later on.
By Joseph Raevis, MD, Jonathan S. Chang, MD


Joseph Raevis, MD


Jonathan S. Chang, MD


Paul Hahn, MD, PhD

Cannula placement in pars plana vitrectomy is routine, but significant complications may potentially occur with malpositioning. A cannula tip placed in the subretinal (*Figure*) or suprachoroidal space may cause air or fluid to enter these regions, creating a surgical challenge. Here, we discuss the operative field and explain corrective measures.

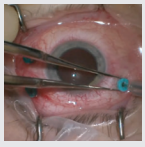
The ora serrata is 7 to 8 mm posterior from the limbus, and nasally is 1 mm more anterior than the temporal side due to postnatal growth.[1] Some patients may have an anteriorly inserted retina. Cannulas are typically placed around 4 mm from the limbus in phakic patients and 3 to 3.5 mm in pseudophakic patients.

Confirming cannula tip location

Malpositioned superior cannulas typically affect the light pipe and vitrector and are noticeable once you insert the instruments. The retina will move with the instruments. A malpositioned infusion cannula may be more difficult to detect. These techniques can confirm the infusion tip's location:

- Direct visualization using the external light pipe and/or the microscope, indenting the eye with the infusion line as needed to visualize.[2,3]
- When dealing with traumatic cataracts or endophthalmitis, a partially inserted light pipe within the infusion cannula may help determine the cannula tip location. Light from a light pipe within the suprachoroidal space results in a reddish-brown light, while a correctly placed cannula reveals white light.[3]

View the Video


Watch as Drs. Raevis and Chang manage infusion line challenges during retinal detachment surgery. Available at: https://bit.ly/VideoPearl_017

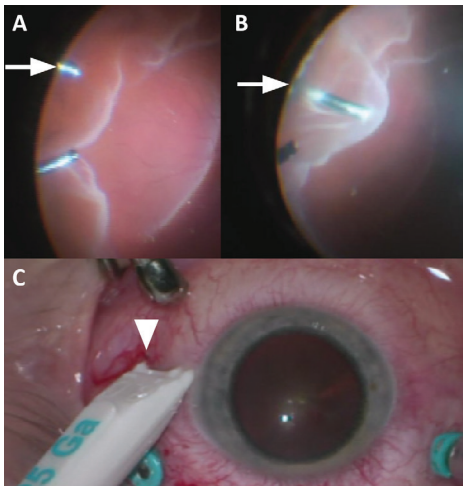


Figure. A bullous retinal detachment (A) with the infusion cannula tip (arrow) in the vitreous cavity at the start of the case. Scleral depression (B) shows the detachment is more bullous and the infusion cannula (arrow) malpositioned in the subretinal space. The original infusion cannula entry site (C, arrowhead) was placed correctly but had to be removed and replaced more anteriorly because of the anatomy.

Intraoperative malposition

Even if the infusion line is correctly placed at the start of the case, scleral depression, eyelid anatomy or a long sclerotomy tunnel can cause the cannula to shift. The former may cause mechanical malposition or retraction as the eye is rotated or the cannula is torqued. If the infusion cannula is too close to the inferior eyelid, rotating the eye inferiorly may cause the infusion line to contact the lower lid, rotating or retracting the infusion cannula. A long sclerotomy tunnel decreases the length of cannula in the intraocular space and can also cause displacement into the subretinal or suprachoroidal space with only minimal retraction.

With a misplaced infusion line, subretinal infusion fluid can cause iatrogenic breaks, tears or retinal detachment. Subretinal air

(Continued on page 34)

Bios

Drs. Raevis and Chang are with the department of ophthalmology and visual sciences at the University of Wisconsin, Madison.

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

DISCLOSURES: Drs. Raevis, Chang and Hahn have no relevant relationships to disclose.

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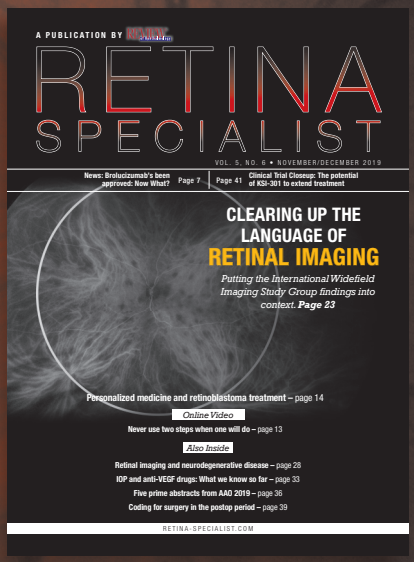

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New Insights for Diabetic Eye Disease

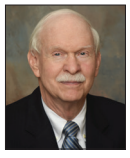
Clinical trial lessons for managing diabetic retinopathy

Key clinical trials can help us determine how to individualize treatment plans for patients with diabetic retinopathy.

By Nidhi Relhan Batra, MD, Nicolas A. Yannuzzi, MD, and Harry W. Flynn Jr., MD

Nidhi Relhan Batra, MD

Nicolas Yannuzzi, MD



Harry W. Flynn Jr. MD

Take-home points

- For eyes with moderately severe to severe nonproliferative diabetic retinopathy, PANORAMA reported lower rates of more than or equal to two-step progression on Diabetic Retinopathy Severity Scale score in the treatment arms.
- For center-involved diabetic macular edema affecting visual acuity, prospective clinical trials have shown the benefit of intravitreal pharmacotherapies.
- DRCR Retina Network Protocol S reported that patients treated with either panretinal photocoagulation or ranibizumab therapy had similar outcomes in visual-field loss and visual acuity after five years.
- Intravitreal anti-VEGF therapies, including bevacizumab, ranibizumab and aflibercept, have shown improvement in visual acuity compared to baseline at two-year follow-up.
- DRCR Retina Network Protocol U reported that addition of an intravitreal dexamethasone implant to continued ranibizumab does not improve VA at 24 weeks compared to ranibizumab alone in eyes with persistent DME.

Treatment strategies for diabetic retinopathy can vary based on disease severity. Some patients may need prompt treatment. Others can be safely observed depending upon their ability to comply with regular and frequent follow-up eye examinations.

Current first-line treatments for proliferative DR and diabetic macular edema are laser and intravitreal injection of both approved and off-label drugs (anti-VEGF, dexamethasone and fluocinolone acetonide of the former; bevacizumab and triamcinolone acetonide of the latter).[1,2]

Ongoing clinical trials and previous landmark study results provide important insights that help retina specialists determine the most effective management strategies. Here, we discuss outcomes of several important clinical trials.

Scope of the problem

The Centers for Disease Control and Prevention reports that 26.9 million people of all ages—8.2 percent of the U.S. population—have been diagnosed with diabetes mellitus, 90 to 95 percent of whom are classified as having type 2 diabetes.[3] DR (including DME and proliferative DR, *Figures 1 and 2*) is one of the most common end-organ manifestations of diabetes.[4]

Take homes from PANORAMA

It's well known that patients with nonproliferative DR are at risk of progressing to vision-threatening events, including PDR and DME. The Phase III prospective, multicenter, randomized, controlled PANORAMA trial evaluated intravitreal aflibercept injections (IAI; Eylea, Regeneron Pharmaceuticals) vs.

observation for patients with moderately severe to severe NPDR.[5]

This double-masked study enrolled 402 patients with NPDR (Diabetic Retinopathy Severity Scale [DRSS] level 47 and 53 confirmed by the central reading center), in whom panretinal photocoagulation could be safely deferred for up to six months. The study had three groups: sham; group 1, IAI q16 weeks; and group 2, IAI q8 weeks. All IAI patients received monthly loading doses for three to five months. The sham group didn't receive IAI loading doses, although group 1 received three initial monthly doses as well as one q8-week interval dose, while group 2 received five monthly doses at the start of treatment. During the second year, group 1 (q16 weeks) continued to receive q16-week IAI, although group 2 (q8 weeks) received *pro re nata* q8-week IAI.

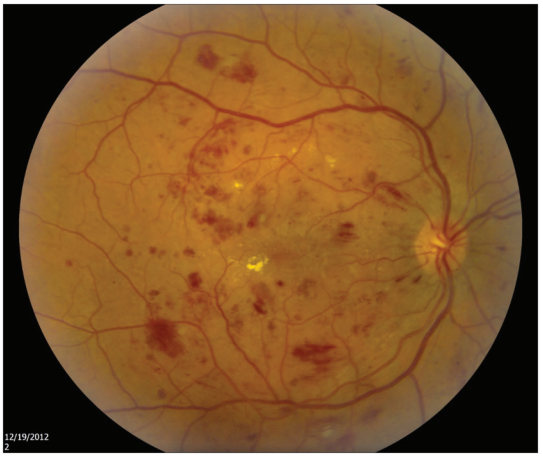


Figure 1. Severe nonproliferative diabetic retinopathy and macular edema.

At two years of follow-up, the percentage of patients with a two-step or greater improvement on DRSS score from baseline (the primary study endpoint) was significantly higher in the IAI groups (50 and 60.2 percent in groups 1 and 2, respectively, vs. 12.8 percent). The trial confirmed that moderately severe to severe NPDR has significant risk of progressing to vision-threatening complications (VTC), including PDR, anterior segment neovascularization (ASNV) and center-involving DME (ci-DME).

The analysis showed a larger number of sham patients (30.6 percent) compared to IAI groups (9.1 and 6.9 percent in groups 1 and 2, respectively) developed VTC at two years. These complications tended to occur more frequently in patients with higher baseline DRSS scores.

The study results are encouraging, but patient compliance and regular follow-ups for multiple injections—at least six to nine in the first year—are mandatory. It's important for patients to understand that these intravitreal injections improve the DRSS scores but do not have a major impact on visual acuity outcome.

Laser vs. intravitreal therapy

The Early Treatment Diabetic Retinopathy Study[6] results, first published in 1985, provided outcomes data on the role of focal- or grid-laser photocoagulation therapy on DME. In the pre-optical coherence tomography era, the ETDRS defined clinically significant macular edema (CSME) as retinal edema involving or threatening the center of the macula. The ETDRS showed 50 percent or greater reduction in the rates of moderate vision loss (MVL, equivalent to a doubling of the visual angle) in laser-treated eyes with CSME compared to untreated control eyes.

With the advent of OCT, our understanding of retinal pathology has improved tremendously. In the current OCT era, various clinical trials and DRCR Retina Network studies have utilized OCT to evaluate DME based on macular thickening of the central subfield. DME can be divided into two

Bios

Dr. Batra is with the department of ophthalmology at Tulane University, New Orleans.=

Drs. Yannuzzi and Flynn are with the department of ophthalmology at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

DISCLOSURES: Dr. Flynn is a member of the DRCR Retina Network data and safety monitoring committee. The statements made and opinions expressed here are personal and do not represent official statements from the DRCR Retina Network.

Drs. Batra and Yannuzzi have no financial relationships to disclose.

types: ci-DME and non-ci-DME.

Level I evidence supports focal/grid-laser treatment vs. no treatment for nci-DME. However, for ci-DME affecting visual acuity, a number of prospective clinical trials—VIVID/VISTA, RISE/RIDE, DRCR Retina Network Protocol T and RESTORE—have shown the beneficial role of intravitreal pharmacological agents to maintain or improve vision as well as anatomy on OCT. [7-10]

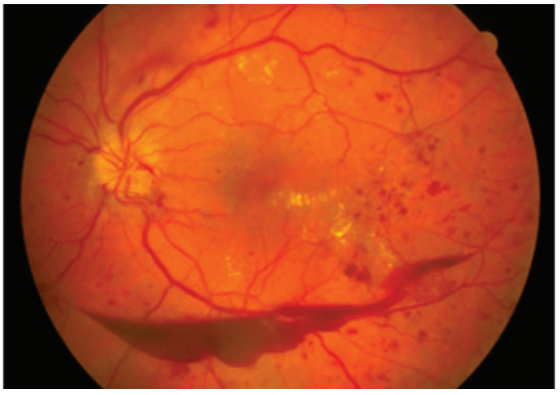


Figure 2. Proliferative diabetic retinopathy with preretinal hemorrhage.

In the DRCR Retina Network Protocol S study, visual-field loss and visual-acuity outcomes were similar in the pan-retinal photocoagulation and ranibizumab arms at five years.

DRCR Retina Network Protocol S

This study evaluated the noninferiority of intravitreal ranibizumab (Lucentis, Roche/Genentech) compared with PRP in patients with PDR.[11-14] This was a multicenter, randomized clinical trial conducted at 55 U.S. sites with 394 study eyes of 305 participants with PDR, VA 20/320 or better, and no history of PRP enrolled between February and December 2012 (mean age, 52 years; 44 percent female; 52 percent white).

Enrolled eyes were randomly assigned to receive PRP treatment, completed in one to three visits (n=203 eyes), or intravitreal ranibizumab 0.5 mg/0.05 ml at baseline and as frequently as q4 weeks based on a structured retreatment protocol (n=191 eyes). Eyes in both treatment groups could receive ranibizumab for DME. At two-year follow-up, mean VA letter improvement (primary outcome) was +0.2 in the PRP group vs +2.8 in the ranibizumab group.

It's important to note that one eye in the ranibizumab group developed endophthalmitis. And at five years, visual-field loss was similar in the PRP and ranibizumab arms, as were VA outcomes.

DRCR Retina Network Protocol T

This study compared currently available anti-VEGF agents among DME eyes with baseline VA of 20/32 to 20/40.[15] All three agents achieved a similar VA gain of approximately 1.5 lines at six months and maintained these gains through two years. For eyes with baseline VA 20/40 or better, visual outcomes were similar for all three anti-VEGF groups. However, among eyes with baseline VA of 20/50 or worse, while all three medications achieved robust VA gains—2 to 3 lines by month six and 24—aflibercept achieved both the greatest VA gain and largest central subfield thickness (CST) reduction.

Although aflibercept outperformed ranibizumab for visual outcomes at one year in eyes with worse baseline VA, no significant visual or anatomic differences between the two drugs were noted at year two. A post-hoc analysis of data of these patients showed that CST changes didn't correlate well with VA changes.

DRCR Retina Network Protocol U

This Phase II randomized clinical trial compared treatment with ranibizumab alone and ranibizumab plus intravitreal dexamethasone implant (Ozurdex, Allergan) in 116 patients with persistent DME.[16] Mean (standard deviation) improvement in visual acuity was 2.7 letters (9.8) in the combination group and 3 letters (7.1) letters in the ranibizumab group (p=0.73), while mean (SD) change in CST in the combination group was a

loss of 110 µm (86) compared with a loss of 62 µm (97) for the ranibizumab-only group ($p<0.001$).

Nineteen eyes (29 percent) in the combination group experienced increased intraocular pressure or initiated treatment with antihypertensive eyedrops compared with none in the ranibizumab group (two-sided, $p<0.001$).

This study concluded that the addition of intravitreal dexamethasone to ranibizumab therapy doesn't improve visual acuity at 24 weeks more than ranibizumab therapy alone among eyes with persistent DME following anti-VEGF therapy.

DRCR Retina Network Protocol V

Protocol V evaluated eyes with ci-DME and very good VA defined as a Snellen equivalent of 20/25 or better (electronic-ETDRS letter score >79).[17] This study reported no significant difference in VA loss at two years, regardless whether eyes were initially managed with aflibercept, laser photocoagulation or observation.

The data disclosed that patients with ci-DME and very good visual acuity can be safely monitored for worsening of visual acuity before treatment.

Bottom line

We should consider all treatment options, keeping in mind the patient-specific factors, including anticipated visit compliance, cost and frequency of visits. In clinical practice, noncompliance among DR patients isn't uncommon and may be caused by doctor visit fatigue secondary to multiple comorbidities, poor diabetes control, insurance issues, transportation difficulties and other factors. The treatment plan should be individualized and guided with the patient's best interests in mind. RS

REFERENCES

1. Relhan N, Flynn HW Jr. The Early Treatment Diabetic Retinopathy Study historical review and relevance to today's management of diabetic macular edema. Curr Opin Ophthalmol. 2017;28:205-212.
2. Bakri SJ WJ, Regillo CD et al. Evidence-Based Guidelines for Management of Diabetic Macular Edema. J VitreoRetinal Dis. 2019;3:145-152.
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2020. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf Updated February 14, 2020. Accessed March 27, 2020.
4. Solomon SD, Chew E, Duh EJ, et al. Erratum. Diabetic retinopathy: A position statement by the American Diabetes Association. Diabetes Care. 2017;40:412-418.
5. Wykoff CC. PANORAMA: A Phase 3, double-masked, randomized study of efficacy and safety of aflibercept in patients with moderate to severe NPDR: Week 100 results. Paper presented at Angiogenesis, Exudation and Degeneration 2020; February 8, 2020; Miami, FL.
6. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103:1796-1806.
7. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013;120:2013-2022.
8. Wykoff CC, Marcus DM, Midena E, et al. Intravitreal aflibercept injection in eyes with substantial vision loss after laser photocoagulation for diabetic macular edema: Subanalysis of the VISTA and VIVID randomized clinical trials. JAMA Ophthalmol. 2017;135:107-114.
9. Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. Ophthalmology. 2016;123:2376-2385.
10. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118:615-625.
11. Bressler SB, Beaulieu WT, Glassman AR, et al. Photocoagulation versus ranibizumab for proliferative diabetic retinopathy: Should baseline characteristics affect choice of treatment? Retina. 2019;39:1646-1654.
12. Hutton DW, Stein JD, Glassman AR, Bressler NM, Jampol LM, Sun JK, for the DRCR Retina Network. Five-Year Cost-effectiveness of intravitreous ranibizumab therapy vs panretinal photocoagulation for treating proliferative diabetic retinopathy: A secondary analysis of a randomized clinical trial. JAMA Ophthalmol. 2019:137:1424-1432.
13. Glassman AR, Beaulieu WT, Stockdale CR, et al. Effect of telephone calls from a centralized coordinating center on participant retention in a randomized clinical trial. Clin Trials. Published online January 27, 2020.
14. Maguire MG, Liu D, Glassman AR, et al., for the DRCR Retina Network. Visual field changes over 5 years in patients treated with panretinal photocoagulation or ranibizumab for proliferative diabetic retinopathy. JAMA Ophthalmol. 2020.
15. Bressler NM, Odia I, Maguire M, et al., for the DRCR Retina Network. Association between change in visual acuity and change in central subfield thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or ranibizumab: A post hoc analysis of the Protocol T randomized clinical trial. JAMA Ophthalmol. Published online June 27, 2019.
16. Maturi RK, Glassman AR, Liu D, et al., for the Diabetic Retinopathy Clinical Research Network. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: A DRCR Network Phase 2 randomized clinical trial. JAMA Ophthalmol. 2018;136:29-38.
17. Baker CW, Glassman AR, Beaulieu WT, et al., for the DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: A randomized clinical trial. JAMA. 2019;321:1880-1894.

We should consider all treatment options, keeping in mind the patient-specific factors, including anticipated visit compliance, cost and frequency of visits.

Retina Debate:

Is navigated laser the answer for DME?

Its use to treat diabetic macular edema has increased, but not without controversy. These two experts debate its merits.

By Jay Chhablani, MD, and Jeffrey K. Luttrull, MD

Jay Chhablani, MD

Jeffrey K. Luttrull, MD

Bios

Dr. Luttrull is a vitreoretinal specialist in private practice in Venture, Calif.

Dr. Chhablani is an associate professor at the University of Pittsburgh School of Medicine, specializing in medical retina and vitreoretinal surgery.

DISCLOSURES: Dr. Chhablani reported financial relationships with Allergan, Novartis and OD-OS (Navilas).

Dr. Luttrull disclosed equity relationships with Ojai Retinal Technologies, Retinal Protection Sciences (RPS) and Replenish Inc., as well as management relationships with Ojai and RPS. He's also founder and executive director of LIGHT: The International Retinal Laser Society.

When navigated laser therapy for retinal disorders first emerged more than a decade ago, it had the potential to eliminate a potentially fallible human element—the retina specialist manually applying laser spots—and replace it with a computer assist to target the laser pulses more precisely to where they were needed. The concept was to combine diagnostic imaging and laser therapy in one system, which gave rise to the Navilas navigated retina laser (OD-OS), approved for U.S. use in 2015.

However, as with any new technology, navigated laser photocoagulation hasn't been without controversy. We have authored multiple publications on laser photocoagulation—in a few cases as coauthors. Here, we take opposite sides of the argument that navigated laser has great potential as a treatment for diabetic macular edema.

PREMISE: Patterns (grids) in laser photocoagulation are beneficial.

Pro, Dr. Chhablani: Pattern laser helps to administer the laser patterns to achieve the therapeutic effect (as in macular laser), as well as to enhance the speed (as in peripheral laser). With Navilas, you have the option to accurately plan the treatment with each single spot if needed.

In some cases they might be forming a "grid" for quick application, making an optimal fit to the pathology. With Navilas, spacing between the laser spots can be modified, or even reduced, to overlapping spots to achieve therapeutic effect.

Con, Dr. Luttrull: Patterns—grids, originally—were used to allow photocoagulation of broad areas of retina while preserving enough function to prevent profound visual loss. Modern retinal laser therapy (MRT) instead improves retinal and visual function directly where it's applied and faces no such constraint.

MRT directly treats all dysfunctional retina confluently to maximize the clinical benefits. Patterns (low-density treatment) thus, at worst, result in under-treatment and, at best, serve no useful purpose.

PREMISE: Differently shaped and sized patterns offer advantages.

Pro, Dr. Chhablani: Preplanned patterns for macular and peripheral lasers help to administer preferred laser patterns for specific lesions, such as grid, lattice degeneration, retinal holes and panretinal photocoagulation. Patterns could be made as the spacing, numbers and shape require.

So, with a single foot press you get what you planned. For DME, this allows for

planning different-sized laser spots (for example, smaller burns for microaneurysms close to the fovea) and patterns for optical coherence tomography-thickness map-guided laser to the area of edema.

Con, Dr. Luttrull: Virtually every current laser platform offers pattern-scanning modes. All offer preset patterns of various shapes and sizes. Some allow the creation of customized patterns. Different pattern sizes and shapes imply a perceived utility to localized treatment. However, focal and local treatments are artifacts of the photocoagulation era required to limit retinal damage and visual loss, and MRT doesn't employ them.

As noted, MRT improves retinal function directly where it's applied. Further, DME is a local manifestation of a panretinal (and indeed systemic) disease, the tip of the iceberg. Thus, DME treatment should extend well beyond the DME itself; panmacular treatment at minimum, preferably the entire retina, is ideal, much the same as drug treatment (*Figure 1, page 24*). Use of variously shaped patterns results in undertreatment and suboptimal results. It's a retinopathy. Treat it. All of it.

'Modern Retinal Laser Therapy'

To assess the value of pattern-scanning and navigated retinal laser systems and subthreshold lasers, a review of our current understanding of retinal laser therapy is in order. Over the past 40 years, we've made great progress toward a sound understanding of the biophysics and mechanisms, and thus the clinical potential, of retinal laser therapy. We call the result "Modern Retinal Laser Therapy" (MRT).[1]

The following facts underpin the principles of MRT and pertain to the place of pattern-scanning and automated laser navigation in 2020:

- All therapeutic retinal laser effects come from cells affected, but not killed, by thermal laser exposure.[1-10]
- Therefore, retinal pigment epithelium preservation is fundamental and essential.
- Therapeutic laser effects are mediated physiologically; they are without adverse effects or tolerance phenomena.[2]
- Therapeutic retinal laser effects arise from acceleration of RPE heat-shock protein (HSP) chaperone kinetics in dysfunctional cells. This normalizes RPE and retinal function independent of the cause of retinal dysfunction, representing a physiological "reset."[5-7]
- As a form of bioactivation (not biomodulation), laser energies exceeding the thermal enzymatic HSP activation threshold don't increase the therapeutic effect, only the risk of damage.[5-7]
- HSP activation kinetics are catalytic and lead to multiple intracellular, local and systemic cascades restorative to retinal function.[1-10]
- Cellular response amplification via recruitment of large areas of dysfunctional retina in confluent laser treatment optimizes therapeutic effects.[4]
- Photocoagulation, or indeed any degree of laser-induced retinal damage, produces no direct therapeutic effects or unique effects different than treatment sublethal to the RPE. By unnecessarily destroying the retina, photocoagulation reduces treatment effectiveness and visual results and is the sole source of all risks, limitations and adverse treatment effects of retinal laser treatment.[1-9] The historical priority of causing photocoagulative retinal damage has given way to retinal-preserving and functionally restorative laser treatments.[3]
- All common laser wavelengths are equally therapeutic, but longer wavelengths are less likely to damage the retina. Near infrared laser is ideal. Shorter, visible wavelengths are best avoided.[7]
- Low-frequency multipulsed lasers are safer and more effective than continuous-wave lasers in some diseases.[7,11,12]

One of the underlying principles of "Modern Retinal Laser Therapy" is that heat-shock protein activation kinetics are catalytic and lead to multiple intracellular, local and systemic cascades restorative to retinal function.

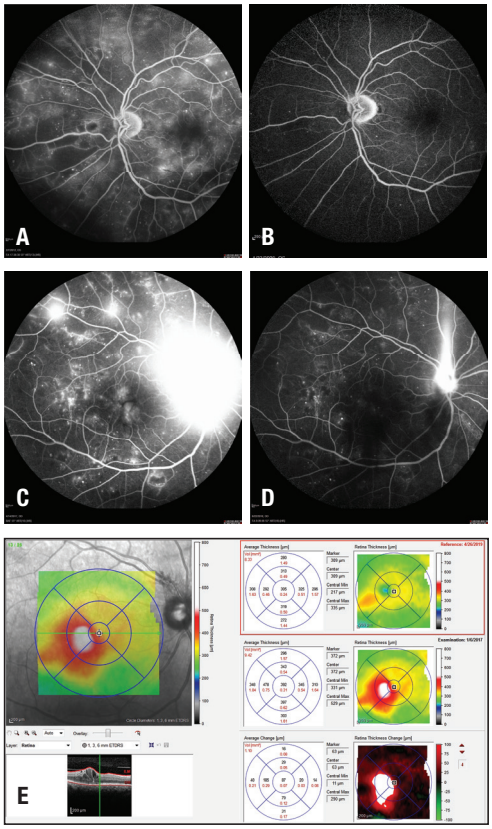


Figure 1. Three eyes of three different patients with various manifestations of diabetic retinopathy, all managed by total-retinal (TR) subthreshold diode micropulse (SDM) as modern retinal laser therapy (MRT) without drug therapy. Top row: Severe nonproliferative diabetic retinopathy before (A) and nine years after (B) TR SDM. Middle row: Severe proliferative DR before (C) and two years after (D) TR SDM. Bottom row: Heidelberg topographical retina map (E) of eye with diabetic macular edema before and two years after TR SDM. As MRT treatment normalizes retinal function without damage or harm, retreatment can be performed anywhere or everywhere, at anytime, as often as necessary (however unlikely). The figures show cases in which the retinopathy was treated anywhere and can be retreated anywhere at anytime, but retreatment isn't likely.

PREMISE: Pattern scanning speeds treatment.

Pro, Dr. Chhablani: I find it very useful, especially in the periphery, as the laser could be very difficult for peripheral lesions. Few patterns hasten the laser process. Yes, preplanning helps to minimize the time of the treatment.

Con, Dr. Luttrull: As a practitioner of MRT, I use identical laser parameters and treatment fields for every eye and every macular indication, including DME (panmacular low-intensity/high-density subthreshold diode micropulse laser, or "SDM"). So, no fiddling with the machine. I just put my foot down on the pedal in the fastest repeat mode and don't lift it until I'm done. Thus, I finish treatment before the typical navigated and/or pattern-scanning user has even planned treatment and prepared their machine.

PREMISE: Documentation of treated areas is important.

Pro, Dr. Chhablani: Documentation is especially important when working with subthreshold laser treatment. In this treatment, the endpoint of the laser isn't visible on ophthalmoscopy. However, a communication on "what has been done" isn't possible (or only based on sketches, which can be inaccurate and often incomplete).

A high risk in subthreshold laser treatment is undertreatment because not enough "area" has been treated, and documentation can help in determining if undertreatment is the cause for no improvement or if the case is simply nonresponsive and other treatment should be considered. In a case of recurrence or poor response, detailed documentation of previous laser treatment helps to plan further treatment. Few providers believe in confluent grid covering the full macular area; however, imaging helps define the "diseased" area. Therefore, I treat only the diseased area with detailed documentation and transparency (*Figure 2*).

Con, Dr. Luttrull: As identifiable MRT lesions are absent (like drug therapy), some laser platforms offer virtual documentation of treatment placement. The implication is that retreatment of a given area is undesirable, or that one needs evidence beyond the therapeutic effect of treatment having been done. The former is obviously relevant only to photocoagulation, which needs no virtual documentation. The latter has never been a concern with drug therapy. As MRT is reliably sublethal to the retina, MRT, like drug therapy, can be repeated infinitely anywhere in the retina, including previously treated areas. There's no reason to know where you've been; only what you want to do next (*Figure 1*).

PREMISE: Focal/laser application improves accuracy.

Pro, Dr. Chhablani: Publications have shown that precise treatment with Navilas helps to improve accuracy and safety.[13] Computerized preplanning allows a precise plan using multimodal imaging before execution. Marked caution zones prevent inadvertent damage to the fovea/optic nerve. Preplanning and live visualization of the laser process allows supervision, which, again, helps to avoid any complication and improves safety.

Con, Dr. Luttrull: Focal/local treatment epitomizes the photocoagulation era. MRT defines photocoagulation as a complication of treatment, and thus a contraindication. Thus, abandoning focal photocoagulation treatment is the best way to improve safety. Once done, pinpoint accuracy is irrelevant. When was the last time you aimed the needle at the DME? MRT, which is sublethal to the RPE and already clinically harmless, isn't made safer or more effective by programmed and limited placement.

PREMISE: Pattern scanning/ navigation reduces treatment time.

Pro, Dr. Chhablani: Pattern scanning/navigation for continuous wave reduces treatment time with increased comfort to the patient as well as reduces re-treatment rate.[14-17] Subthreshold lasers are painless and faster.

Con, Dr. Luttrull: It's shortening continuous-wave photocoagulation spot duration and intensity that reduces pain, not aiming or patterning. However, it also reduces efficacy. MRT is already painless. RS

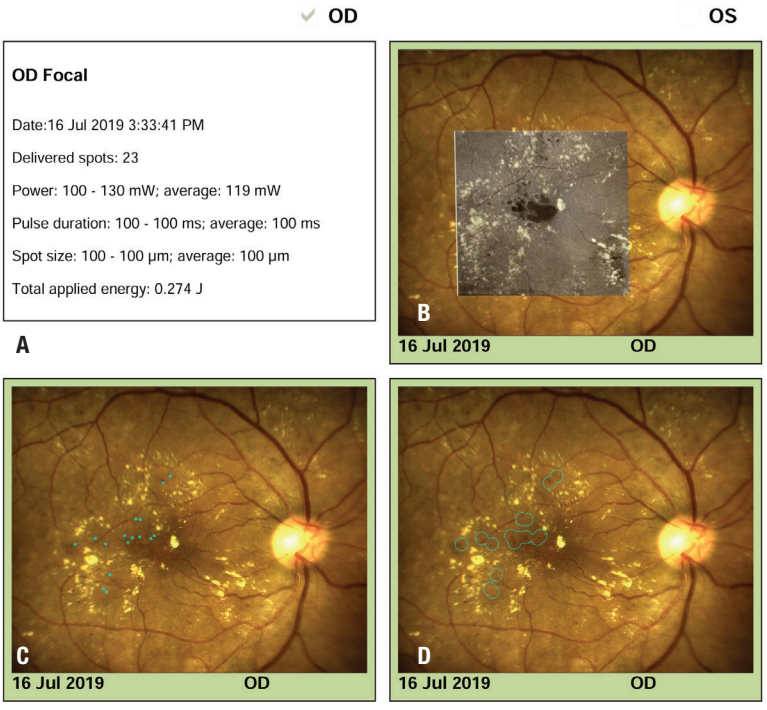


Figure 2. An example of a report after navigated laser photocoagulation for diabetic macular edema. The report (A) includes details about the laser parameters; overlaid fluorescein angiography image on the color fundus photograph (B) obtained with the Navilas system with planned laser spots; planned laser spots on the color fundus photograph (C); and color fundus photography with administered laser spots (D). (*Courtesy Dmitri Matsev, MD, Medical Academy, St. Petersburg, Russia*)

REFERENCES

1. Luttrull JK, Kent D. Modern retinal laser for neuroprotection in open-angle glaucoma. In: Samples JR, Ahmed IIK, eds. New Concepts in Glaucoma Surgery, Vol. 1. Amsterdam; Kugler Publications; 2019. In press.
2. Luttrull JK, Chang DB, Margolis BWL, Dorin G, Luttrull DK. Laser resensitization of medically unresponsive neovascular age-related macular degeneration: Efficacy and implications. Retina. 2015; 35:1184-1194.
3. Chhablani J, Roh YJ, Jobling AI, et al. Restorative retinal laser therapy: Present state and future directions. Surv Ophthalmol. 2018;63:307-328.
4. Luttrull JK, Dorin G. Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: A review. Curr Diabetes Rev. 2012;8:274-284.
5. Kregel K. Heat shock proteins: Modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol. 2002;92:2177-2186.
6. Inagaki K, Shuo T, Katakura K, Ebugara Bm Nyrajanu Am Igjisgu J. Sublethal photothermal stimulation with a micropulse laser induces heat shock protein expression in arpe-19 cells. J Ophthalmol. Published online November 30, 2015.
7. Chang DB, Luttrull JK. Comparison of subthreshold 577nm and 810nm micropulse laser effects on heat-shock protein activation kinetics: Implications for treatment efficacy and safety. Translational Vis Sci Technol. In press.
8. Midena E, Bini S, Martini F, Enrica C, et al. Changes of aqueous humor Müller cells' biomarkers in human patients affected by diabetic macular edema after subthreshold micropulse laser treatment. Retina. 2020;40:126-134.
9. Caballero S, Kent DL, Sengupta N, et al. Bone marrow-derived cell recruitment to the neurosensory retina and retinal pigment epithelial cell layer following subthreshold retinal phototherapy. Invest Ophthalmol Vis Sci. 2017;58:5164-5176.
10. De Cilla S, Vezzola D, Farruggio S, et al. The subthreshold micropulse laser treatment of the retina restores the oxidant/antioxidant balance and counteracts programmed forms of cell death in the mice eyes. Acta Ophthalmol. 2019:97:e559-e567.
11. Chhablani J, Alshareef R, Kim DT, Narayanan R, Goud A, Mathai A. Comparison of different settings for yellow subthreshold laser treatment in diabetic macular edema. BMC Ophthalmol. 2018;18:168.
12. Vujosevic S, Martini F, Longhin E, Convento E, Cavarzeran F, Midena E. Subthreshold micropulse yellow laser versus subthreshold micropulse infrared laser in center-involving diabetic macular edema: Morphologic and functional safety. Retina. 2015;35:1594-1603
13. Kozak I, Oster SF, Cortes MA, et al. Clinical evaluation and treatment accuracy in diabetic macular edema using navigated laser photocoagulator NAVILAS. Ophthalmology. 2011;118:1119-1124.
14. Chhablani J, Mathai A, Rani P, Gupta V, Arevalo JF, Kozak I. Comparison of conventional pattern and novel navigated panretinal photocoagulation in proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci. 2014;55:3432-3438.
15. Kernt M, Cheuteu RE, Cserhati S, et al. Pain and accuracy of focal laser treatment for diabetic macular edema using a retinal navigated laser (Navilas). Clin Ophthalmol. 2012;6:289-296.
16. Neubauer AS, Langer J, Liegl R, et al. Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser. Clin Ophthalmol. 2013;7:121-128.
17. Ober MD, Kernt M, Cortes MA, Kozak I. Time required for navigated macular laser photocoagulation treatment with the Navilas. Graefes Arch Clin Exp Ophthalmol. 2013;251:1049-1053.

More frequent dosing for refractory nAMD?

A closer look at biweekly anti-VEGF dosing for chronic disease that doesn't respond completely to standard monthly dosing.

By Samuel C. Fowler and Eric W. Schneider, MD

Samuel C. Fowler

Eric W. Schneider, MD

Take-home points

- The need exists for a clear and consistent definition of "refractory" or "treatment-resistant" neovascular age-related macular degeneration.
- Biweekly dosing is supported by mathematical modeling of vascular endothelial growth factor-binding activity with different doses and treatment frequencies and short-term optical coherence tomography angiography data that detail the response to anti-VEGF therapy.
- Our small retrospective analysis of patients that received biweekly anti-VEGF therapy for refractory nAMD showed anatomical and visual-acuity improvements compared to baseline.
- Given the limited data available and the relatively high prevalence of refractory disease, there is a need for a prospective evaluation of increased frequency anti-VEGF dosing in patients with refractory nAMD.

Bios

Mr. Fowler is a medical student at the University of Tennessee Health Science Center, Memphis.

Dr. Schneider practices with Tennessee Retina, based in Nashville with offices in central Tennessee and southern Kentucky.

DISCLOSURES: Mr. Fowler has no financial relationships to disclose.

Dr. Schneider is a consultant/speaker for Carl Zeiss Meditec, and a consultant to and receives grant funding from Regeneron Pharmaceuticals.

The original treatment paradigm for neovascular age-related macular degeneration relied on repeated monthly dosing of anti-VEGF agents to achieve optimal visual gain and anatomic resolution of intra- or subretinal fluid on optical coherence tomography imaging.

With the introduction of variable dosing regimens such as "PRN" (*pro re nata*) and "treat-and-extend," patients demonstrating a good response to anti-VEGF therapy can be treated at extended intervals after achieving specific benchmarks, most often resolution of fluid on OCT.[1,2]

A matter of definition

• ***Refractory/treatment-resistant nAMD.*** However, patients who don't meet these benchmarks cannot be extended. They fall into a somewhat ill-defined refractory or treatment-resistant category. The term *refractory nAMD* remains largely fluid in its definition, because it hasn't been constrained to one specific time frame or criteria. Rather, the term is applied to a wide range of findings; the foundation is treatment resistance despite aggressive therapy over an extended period of time.[3]

Some classification systems look to define treatment-resistance as persistent exudation on retinal imaging; others require three or more lines of Snellen acuity loss.[4] In the absence of a consensus, many consider more than 12 months of persistent exudation found on OCT, despite monthly anti-VEGF therapy, to be indicative of treatment-resistant nAMD.[5,6]

Using this latter definition, the size of the refractory nAMD problem comes into view. One-year CATT data demonstrated persistent fluid on OCT despite 12 monthly treatments in 53.2 percent

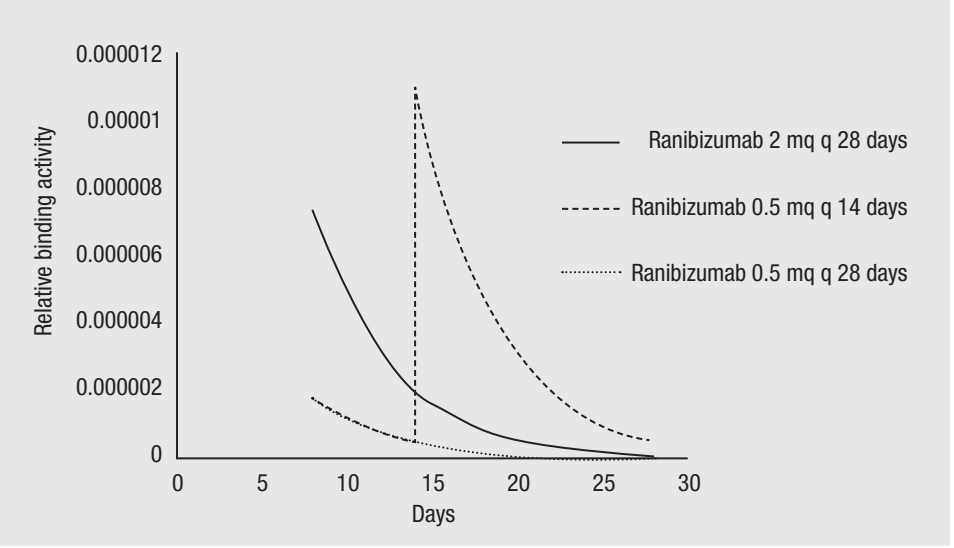


Figure 1. Plot of time-dependent anti-VEGF binding activities of ranibizumab (Lucentis, Genentech/Roche), generated by mathematical modeling, demonstrates higher trough levels using biweekly dosing as compared to monthly dosing with standard or increased doses.[18]

of ranibizumab-treated and 70.9 percent of bevacizumab-treated patients (Lucentis and Avastin, Genentech/Roche). In the VIEW 1 and 2 studies, 27.6 percent of patients had intra- or subretinal fluid (IRF, SRF) after 12 monthly aflibercept injections (Eylea, Regeneron Pharmaceuticals).[7,8] Given the prevalence of this problem, an assessment of treatment options for this challenging population appears warranted.

Anti-VEGF-based approaches

• ***Switching anti-VEGF agents.*** With the proliferation of new anti-VEGF agents, one of the simplest approaches to refractory disease is to switch to a different agent. Various logic has been applied to this approach, from combating theoretical tachyphylaxis to taking advantage of improved binding affinity or superior intravitreal pharmacokinetics.[9-11]

Following the release of aflibercept in 2012, numerous small retrospective studies detailed results of treating nAMD refractory to ranibizumab or bevacizumab with aflibercept.[12,13] Although such small retrospective studies are inherently difficult to interpret, subsequent meta-analyses reported significantly improved anatomic, though not visual, outcomes following a switch to aflibercept.[14,15]

• ***Increasing anti-VEGF dose.*** Investigators have also explored the use of larger anti-VEGF doses as a way to boost efficacy via greater binding site availability. The HARBOR study, which compared ranibizumab 2 mg monthly or PRN to the standard 0.5-mg dose monthly or PRN, found no statistically significant difference in visual or anatomic outcomes in treatment-naïve patients.[7] The subsequent LAST and SAVE studies in "treatment-resistant" populations, however, did show modest visual and anatomical improvements at six months when switching resistant patients from monthly 0.5-mg to 2-mg ranibizumab.[16,17]

• ***Increasing anti-VEGF dosing frequency.*** Similar to increasing the dose of the anti-VEGF agent, increasing the dosing frequency achieves the goal of delivering greater amounts of anti-VEGF binding capacity into the eye. Based on mathematical modeling of time-related binding activities of the various

In the VIEW 1 and 2 studies, 27.6 percent of patients had intra- or subretinal fluid after 12 monthly aflibercept injections.

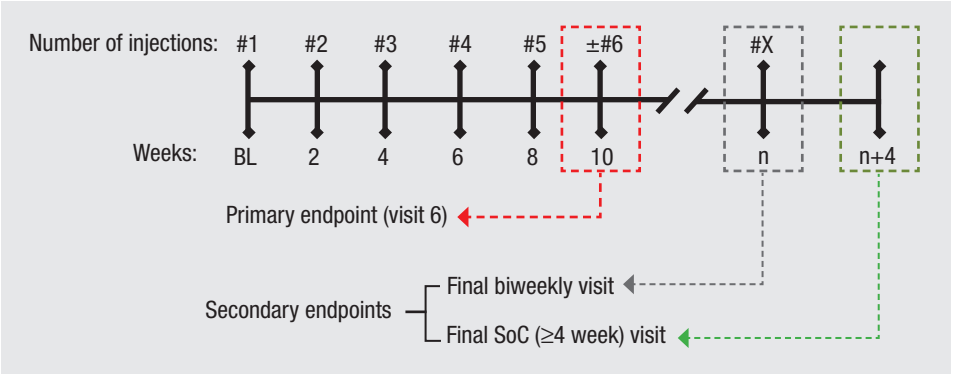


Figure 2. Study schematic illustrating primary and secondary endpoints (SoC=standard of care).

anti-VEGF agents, however, increased dosing frequency (q2 weeks) provides much greater trough levels of drug compared to an increased dose (*Figure 1, page 27*).[18] Given the vast excess of anti-VEGF binding activity at peak levels (e.g., immediately following injection), trough-binding activity likely dictates efficacy.

Further support for increased dosing frequency can be obtained from examination of serial OCT angiography data looking at the choroidal neovascular membrane's response to anti-VEGF therapy. Following anti-VEGF treatment, a maximum decrease in choroidal neovascular dimension and microvascular rarefaction has been seen at 12 to 18 days, with resultant reproliferation noted thereafter.[19]

Two small retrospective studies examined the utility of a short course (three to four doses) of biweekly anti-VEGF therapy for refractory nAMD, with mixed results. An Israeli study didn't find any significant anatomic or visual improvement, with about one quarter of patients demonstrating morphologic improvement.[20] In contrast, Andre Witkin, MD, and colleagues reported that they achieved significant visual-acuity gains and central foveal thickness benefits.[21]

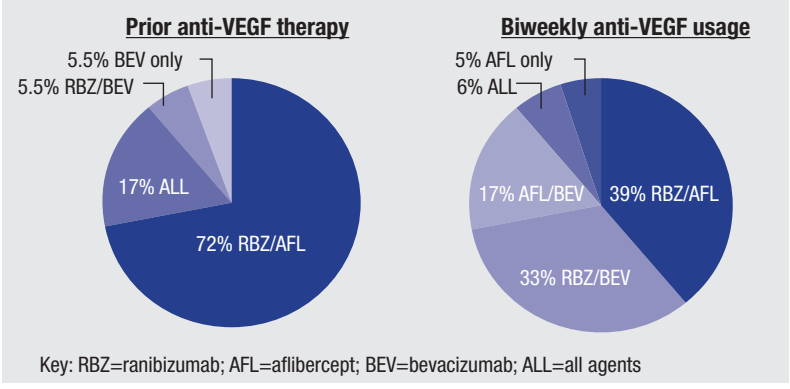


Figure 3. Anti-VEGF use before study entry and during biweekly therapy.

Increased frequency: A deeper dive

In light of the strong rationale for increased dosing frequency and limited available data in the literature, our group designed a retrospective study to analyze outcomes of patients within our practice who had received biweekly anti-VEGF therapy for refractory nAMD. For purposes of this study, we defined refractory nAMD as persistent IRF/SRF observed on spectral-domain OCT following six or more monthly (q28 to 35 days) anti-VEGF injections.

Participating patients had to have received five or more consecutive biweekly anti-VEGF injections (every 12 to 21 days) with a two-week follow-up visit after the fifth biweekly injection and a minimum of 12 months of follow-up after initiation of biweekly therapy. The primary endpoint was two weeks after the fifth consecutive biweekly injection (visit six). In order to assess the impact of a return to standard of care (SoC) monthly dosing, we also reassessed outcomes at both the

I was only seeing light flashes early on, but light

FLASHES

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

—Keith H, retinal prosthesis recipient

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final biweekly and first monthly (≥28 day) follow-up visits (*Figure 2*).

The 18 patients included in this analysis were representative of a chronic refractory nAMD population, with a mean duration of anti-VEGF therapy of 35.4 months. At baseline, five of 18 (27.8 percent) had persistent IRF while 16 of 18 (88.9 percent) had persistent SRF despite a mean inter-treatment interval of 30.9 days over the last three SoC injections.

In terms of biweekly treatment, patients underwent a mean of 18.1 biweekly injections at a mean treatment interval of 16.5 days. Figure 3 (*page 28*) shows the various anti-VEGF agent combinations used prior to and during biweekly therapy.

Results of biweekly therapy

No safety signals were noted during biweekly therapy. From an anatomic standpoint, a significant decrease in central subfield thickness and cube volume was noted at visit six. Both measures remained significantly improved through the final biweekly visit, but only cube volume remained significantly improved upon return to SOC dosing (*Figure 4*).

Analysis of qualitative fluid status revealed biweekly therapy was more effective at eliminating SRF than IRF. Nearly one-third of patients had complete SRF resolution at visit six, while none achieved completed IRF resolution. This effect on SRF waned upon return to SOC dosing. Figure 5 demonstrates the anatomical response of a single included patient to biweekly therapy and highlights the return of SRF upon return to SoC dosing.

Overall, functional improvement was more limited. There was a significant improvement in best-corrected visual acuity at visit six compared to baseline. However, this was not sustained at the final biweekly or first SOC visit.

This study has several limitations, including its small size, retrospective design, heterogeneous biweekly dosing duration/anti-VEGF agent utilization and nonstandard follow-up timing.

Bottom line

The data from our study, as well as that presented by Dr. Witkin and colleagues and the Israeli researchers, suggest improved anatomic and possibly visual outcomes with increased dosing frequency in patients with refractory nAMD.

As noted, these retrospective studies have inherent limitations, particularly related to defining refractory patients in a post-hoc fashion, thus limiting the conclusions that can be drawn. In view of the prevalence of the problem and the limited data available, there appears to be a clear need for a prospective evaluation of increased anti-VEGF dosing frequency.

Trial of biweekly aflibercept

To that end, we undertook an open-label prospective trial of biweekly aflibercept for patients with refractory nAMD. This study defined refractory nAMD as persistent SRF with or without IRF despite five or more monthly aflibercept injections in patients who have had a year or more of monthly anti-VEGF therapy.

In this trial, entitled TRISTAR (for Two-week Retreatment Interval Study for Treated AMD Refractory to monthly aflibercept), patients received six biweek-

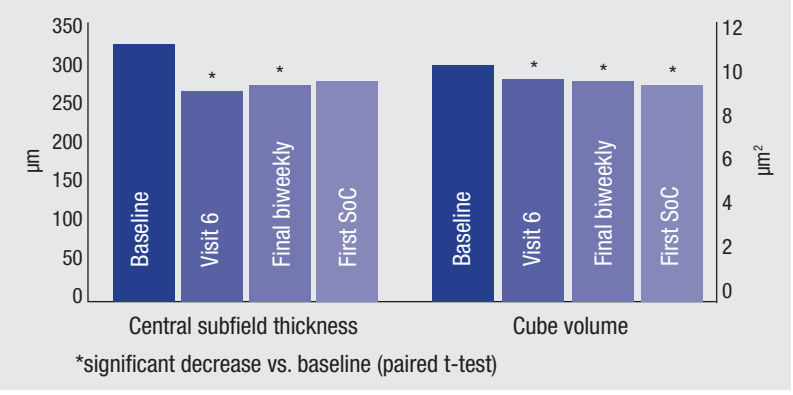


Figure 4. Comparison of central subfield thickness and cube volume at the primary and secondary endpoints demonstrates significant improvement at visit six and the final biweekly visit. This improvement remained significant only for cube volume upon return to standard-of-care (SoC) dosing.

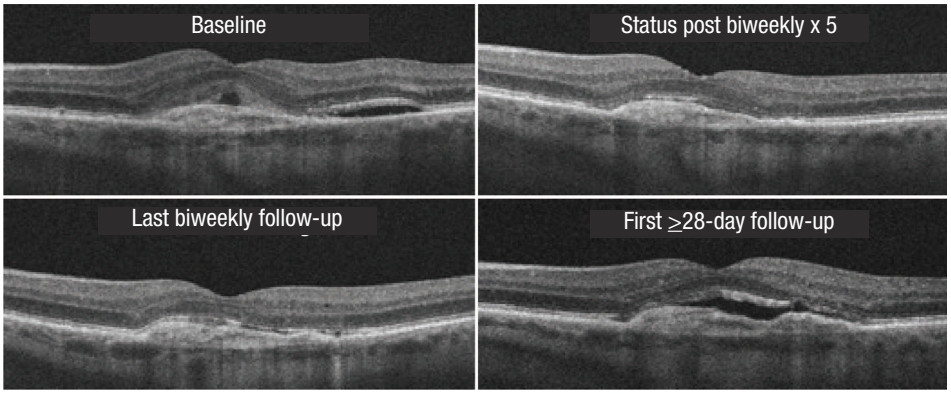


Figure 5. Case study of the anatomic changes of a single enrolled patient. Subretinal fluid is resolved during active biweekly treatment but returns once standard-of-care therapy is reinitiated.

ly aflibercept injections with a secondary randomization into standard monthly therapy vs. four additional biweekly treatments for those with persistent SRF following the initial six biweekly treatments. Regeneron Pharmaceuticals is collaborating on the study.

The study enrolled 22 patients with the last patient/last visit in November 2019. The data are currently being analyzed with a plan to present the results at an upcoming meeting. It's our hope that these data can clarify the utility of increased anti-VEGF dosing frequency in this challenging patient population.

REFERENCES

1. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J ophthalmol. 2007;143:566-583.
2. Engelbert M, Zweifel SA, Freund KB. Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified "treat and extend" dosing regimen of intravitreal antivascular endothelial growth factor therapy. Retina. 2010;30:1368-1375.
3. Schachat AP. Switching anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration. Am J Ophthalmol. 2013;156:1-2.e1.
4. Broadhead GK, Hong T, Chang AA. Treating the untreatable patient: current options for the management of treatment-resistant neovascular age-related macular degeneration. Acta Ophthalmol. 2014;92:713-723.
5. Chang AA, Li H, Broadhead GK, et al. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. Ophthalmology. 2014;121:188-192.
6. Kumar N, Marsiglia M, Mrejen S, et al. Visual and anatomical outcomes of intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with ranibizumab in patients with neovascular age-related macular degeneration. Retina. 2013;33:1605-1612.
7. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2014;121:2181-2192.
8. Jaffe GJ, Ying GS, Toth CA, et al, for the Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Macular morphology and visual acuity in year five of the Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology. 2019;126:252-260.
9. Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology. 2008;115:2199-2205.
10. Gasperini JL, Fawzi AA, Khondkaryan A, et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol. 2012;96:14-20.
11. Lazzeri S, Ripandelli G, Sartini MS, et al. Aflibercept administration in neovascular age-related macular degeneration refractory to previous anti-vascular endothelial growth factor drugs: a critical review and new possible approaches to move forward. Angiogenesis. 2015;18:397-432.
12. Bakall B, Folk JC, Boldt HC, et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. Am J ophthalmol. 2013;156:15-22.e11.
13. Yonekawa Y, Andreoli C, Miller JB, et al. Conversion to aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. Am J Ophthalmol. 2013;156:29-35.e22.
14. Spooner K, Hong T, Wijeyakumar W, Chang AA. Switching to aflibercept among patients with treatment-resistant neovascular age-related macular degeneration: a systematic review with meta-analysis. Clin Ophthalmol. 2017;11:161-177.
15. Seguin-Greenstein S, Lightman S, Tomkins-Netzer O. A meta-analysis of studies evaluating visual and anatomical outcomes in patients with treatment resistant neovascular age-related macular degeneration following switching to treatment with aflibercept. J Ophthalmol. Published online March 6, 2016.
16. Fung AT, Kumar N, Vance SK, et al. Pilot study to evaluate the role of high-dose ranibizumab 2.0 mg in the management of neovascular age-related macular degeneration in patients with persistent/recurrent macular fluid <30 days following treatment with intravitreal anti-VEGF therapy (the LAST Study). Eye (Lond). 2012;26:1181-1187.
17. Brown DM, Chen E, Mariani A, Major JC Jr for the SAVE Study Group. Super-dose anti-VEGF (SAVE) trial: 2.0 mg intravitreal ranibizumab for recalcitrant neovascular macular degeneration-primary end point. Ophthalmology. 2013;120:349-354.
18. Stewart MW, Rosenfeld PJ, Penha FM, et al. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). Retina. 2012;32:434-457.
19. Lumbroso B, Rispoli M, Savastano MC. Longitudinal optical coherence tomography–angiography study of type 2 naive choroidal neovascularization early response after treatment. Retina. 2015;35:2242-2251.
20. Mimouni M, Meshi A, Vainer I, et al. Bevacizumab dosing every 2 weeks for neovascular age-related macular degeneration refractory to monthly dosing. Jpn J Ophthalmol. 2018;62:652-658.
21. Witkin AJ, Rayess N, Garg SJ, et al. Alternating bi-weekly intravitreal ranibizumab and bevacizumab for refractory neovascular age-related macular degeneration with pigment epithelial detachment. Semin Ophthalmol. 2017;32:309-315.

Retina Standouts from ARVO 2020

New revelations for nAMD, CSC treatments and ILM utility

Trial readouts on improving treatment durability, a potential new therapy for central serous chorioretinopathy and adding to the debate of RRD repair.

By Ashkan M. Abbey, MD

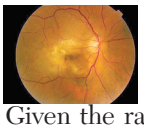
Ashkan M. Abbey, MD

Take-home points

- Three emerging therapies have shown potential durability in prolonging treatment intervals for age-related macular degeneration.
- Central serous chorioretinopathy in some patients responded to treatment with systemic PDE5/6 inhibitor sildenafil.
- Retrospective review of 1,200-plus rhegmatogenous retinal detachment repairs reports similar outcomes with and without internal limiting membrane peeling.

The coronavirus pandemic may have forced the cancellation of this year's meeting of the Association for Research in Vision and Ophthalmology, but the call was made late after all those ARVO abstracts had been submitted, reviewed and accepted —and published online.

Here, we present our annual selection of five compelling posters and presentations. We begin with three promising therapies designed to significantly reduce the treatment burden for neovascular age-related macular degeneration. The last two abstracts discuss sildenafil as a potential treatment for central serous chorioretinopathy (CSC) and the utility of internal limiting membrane peeling for repair of rhegmatogenous retinal detachments.



First in-human results of single-injection sunitinib

Given the rapidly increasing aging population, the need for increased durability to reduce treatment burden for nAMD has become paramount. Sunitinib, a pan-vascular endothelial growth factor receptor inhibitor, has been formulated as an intravitreal depot (GB-102, Graybug Vision) designed to increase treatment intervals to every six months or more.

ADAGIO is a multicenter, open-label, escalating dose-cohort Phase I/IIa study of 32 patients who've had nAMD for less than 18 months.[1] All patients received at least three prior anti-VEGF injections and demonstrated response to treatment. Intravitreal GB-102 was administered at a dose of 0.25, 0.5, 1 or 2 mg, and the patients were then followed monthly for eight months. If certain criteria were met, they received supportive aflibercept (Eylea, Regeneron Pharmaceuticals) therapy.

At baseline, mean best-corrected visual acuity was 63.3 letters and mean central subfield thickness 294 µm. Patients received an average of 4.8 anti-VEGF treatments before enrollment.

Bios

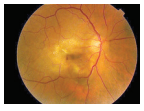
Dr. Abbey is a surgical and medical retina specialist at Texas Retina Associates, Dallas, and clinical assistant professor of ophthalmology at the University of Texas Southwestern Medical Center.

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

The presence of transient medication residue was the most frequently reported adverse event (n=9). The proportion of patients that did not require additional supportive anti-VEGF treatment at three, six and eight months was 88, 68 and 42 percent, respectively. No dose-limiting toxicities, ocular serious adverse events or infections were reported.

Existing anti-VEGF treatments permit treatment intervals of up to three months in certain patients. GB-102 maintained an acceptable level of disease activity in a cohort of nAMD patients for up to eight months without additional treatment. GB-102 demonstrated potential to reduce treatment burden in nAMD, but further study is warranted.

Disclosures: Lead author Charles Semba is an employee of Graybug Vision, and four coauthors disclosed financial relationships with Graybug.



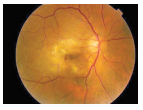
IVT gene therapy suppresses disease activity to 11 months

ADVM-022 (AAV.7m8 aflibercept gene therapy, Adverum Biotechnologies) is an intravitreal gene therapy designed to provide sustained therapeutic levels of aflibercept after a single injection. The OPTIC Trial is an open-label, multicenter, dose-ranging study in previously treated nAMD patients with confirmed response to anti-VEGF therapy.[2] A single intravitreal injection of ADVM-022 was administered at $6x10^{11}$ vg/eye in cohort 1 (n=6) and $2x10^{11}$ vg/eye in cohort 2 (n=6). Patients meeting certain criteria would receive rescue aflibercept therapy.

Cohort 1 patients required a mean of 6.2 anti-VEGF injections in the eight months prior to enrollment to maintain their baseline mean BCVA of 65.8 letters. Any postinjection inflammation was generally anterior, mild and manageable with topical steroids. At a median of 34 weeks of follow-up (range: 24 to 44 weeks), no patients required rescue injections. No dose-limiting toxicities, serious ocular adverse events or endophthalmitis were reported.

ADVM-022 maintained an acceptable level of disease activity in a cohort of nAMD patients for up to 11 months without additional treatment.[2]

Disclosures: Lead author Arshad M. Khanani, MD, and co-authors disclosed financial relationships with Adverum Biotechnologies, three of whom are employees.



Anti-VEGF biopolymer conjugate extends treatment

The final potential therapeutic agent with increased durability is KSI-301 (Kodiak Sciences), a novel anti-VEGF antibody biopolymer conjugate. In a Phase Ib study, treatment-naïve patients with nAMD, diabetic macular edema or retinal vein occlusion received three initial monthly doses of either 2.5 mg or 5 mg KSI-301.[3] Additional treatment for each disease was based upon protocol-specified retreatment criteria.

Among 55 patients, mean BCVA change at week 20 was +4.3 letters in nAMD (n=25, baseline 64.5), +7.4 letters in DME (n=15, baseline 66.8) and +21.3 letters in RVO (n=15, baseline 54.9). Mean change in CST was -67 µm in nAMD (baseline 426), -129 µm in DME (baseline 449) and -365 µm in RVO (baseline 675).

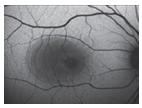
Treatment was extended to three months or longer in 92 percent of nAMD eyes after the last loading dose without retreatment; 72 percent of DME eyes were extended to four months or longer; and half of RVO eyes were extended to three months or longer. In a total of 338 doses, no reports of intraocular inflammation and no drug-related adverse events were noted.

KSI-301 demonstrated excellent efficacy and durability and had no reported cases of intraocular inflammation in this study. If the vision outcomes and safety profile are similar in larger patient cohorts, this could prove to be a very intriguing treatment for multiple common retinal diseases.

Disclosures: Lead author Sunil S. Patel,

GB-102 maintained an acceptable level of disease activity in a cohort of nAMD patients for up to eight months without additional treatment and showed the potential to reduce treatment burden.

MD, is a consultant to Kodiak Sciences, and all coauthors are employees of Kodiak Sciences.



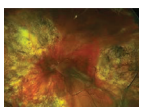
CSC shows treatment response to sildenafil

Oral sildenafil, best known as the erectile dysfunction drug Viagra, is a systemic inhibitor of phosphodiesterase 5 and 6 (PDE5/6). In patients with CSC, it may reduce subretinal fluid and improve vision. Inhibition of PDE5/6 enhances the effects of nitrous oxide, which leads to increased choroidal blood flow. This may accelerate the resorption of SRF in CSC.

Four patients with refractory CSC were treated with oral sildenafil 20 or 40 mg b.i.d. and followed for an average of four months.[4] All patients demonstrated resolution of SRF. Mean time to resolution of SRF was two to three months. Mean improvement in visual acuity was 7 letters.

The authors report that sildenafil was well-tolerated by all patients. Larger studies are warranted, but this may be a promising new agent for the treatment of chronic and/or recurrent CSC.

Disclosures: The study authors have no relationships to report.



ILM peeling during RRD surgery

Recent publications have led retina specialists to debate the need for concurrent peeling of the ILM during pars plana vitrectomy for RRD. Some believe that ILM peeling can reduce the rate of postoperative epiretinal membrane and proliferative vitreoretinopathy formation. Matthew Starr, MD, and colleagues performed a multi-institutional retrospective review of all RRD surgeries involving PPV for a full calendar year (2015) and compared the outcomes between eyes with and without ILM peeling.[5]

The series included 1,287 eyes, 87 (6.8 percent) of which underwent ILM peeling at the time of surgery. Final mean visual acuity was significantly better in the group without ILM peeling (logMAR 0.44 ±0.57, Snellen 20/55) vs. eyes with ILM peeling (logMAR 0.64 ±0.66, Snellen 20/87, p=0.0096).

A multivariate analysis that accounted for four preoperative factors—VA, PVR, and macular hole and macular attachment status—found no difference in postoperative visual acuity between eyes with and without ILM peeling (p=0.2373).

The single-surgery success rate was not significantly different between the two groups: 86.2 percent with ILM peeling vs. 83 percent without (p=0.5571). The rate of postoperative ERM formation was also not significantly different: 29.1 percent vs. 35.7 percent, respectively, (p=0.1330).

The debate continues regarding the utility of ILM peeling in RRDs. This large retrospective review should give us pause when deciding to peel the ILM in PPVs for RRDs, but we need more robust prospective data.

Disclosures: The study authors have no relationships to report.

REFERENCES

1. Semba C, Patel SS, Kunimoto DK, et al. A novel intravitreal depot formulation of sunitinib (gb-102): Eight-month results of a Phase I/IIa first-in-human single injection study in patients with neovascular age-related macular degeneration (ADAGIO Study). Association for Research in Vision and Ophthalmology 2020 abstract #4918-B0123.
2. Khanani AM, Kiss S, Turpcur A, Hoang C, Osborne A. Phase 1 Study of Intravitreal Gene Therapy ADVM-022 for Neovascular AMD (OPTIC Trial). ARVO 2020 abstract #1154.
3. Patel SS, Janer D, Miller B, Perloth V, Valezquez-Martin JP. Updated Results of Phase 1b Study of KSI-301, an Anti-VEGF Antibody Biopolymer Conjugate with Extended Durability, in wAMD, DME, and RVO. ARVO 2020 abstract #4286.
4. Daly S, Coleman DJ, Breazzano M, et al. Central serous chorioretinopathy treatment with a systemic PDE5/6 inhibitor (sildenafil. ARVO 2020 abstract # 1071.
5. Starr M, Patel L, Ammar MJ, et al. Utility of internal limiting membrane peeling during rhegmatogenous retinal detachment surgery. ARVO 2020 Abstract #3527.

Fixing a misaligned cannula

(Continued from page 16)

may make it difficult to flatten the retina. Suprachoroidal infusion of air or fluid may cause a choroidal detachment and present with hypotony.

Fatalities from an air embolus in the lungs or cerebral infarct in conjunction with a patent foramen ovale in the heart have been associated with inadvertent suprachoroidal infusion of air. A porcine model demonstrated that pressurized air from a suprachoroidal infusion tip can enter the vortex veins and systemic circulation.[2] To prevent this, some surgeons recommend reconfirming the infusion tip location just before an air-fluid exchange.

Corrective measures

It's important to identify a misplaced infusion line promptly. Corrective measures include stopping the infusion and repositioning the line either in a different cannula already in place or by removing and replacing the infusion cannula in another location.

Steve Charles, MD, has reported using a micro-vitreoretinal blade to incise any tissue overlying the infusion line. Other techniques include using the smooth forceps to advance a retracted cannula until flush to the sclera, or a 6-mm cannula to help ensure extension of the cannula in the vitreous cavity.

It's important to constantly monitor the infusion line position and address any concerns for malposition.

REFERENCES

1. Schepens C, Bahn G. Examination of the ora serrata: Its importance in retinal detachment. AMA Arch Ophthalmol. 1950;44:677-690.
2. Gayer S, Palte H, Albini T, et al. In vivo porcine model of venous air embolism during pars plana vitrectomy. Am J Ophthalmol. 2016;171:139-144.
3. Shoeibi N, Ansari-Astaneh M. A simple method for detecting vitrectomy infusion line position in hazy media, in case of poor visualization. Retina. 2014;34:1707-1709.

When unhappy patients vent online

How retina specialists can address negative online reviews and unfavorable comments on social media.

Sooner or later, to your surprise or dismay, you will be the subject of a negative online review. Whether it's on Yelp, Facebook or one of the specialized physician-rating websites, unhappy patients have a multitude of ways to express their dissatisfaction. Much as a diner can spit vitriol at a poor restaurant meal, patients now commonly use online reviews to voice opinions of their medical professional.

Don't ever respond online

A *ProPublica/Washington Post* investigation reviewed 1.7 million patient Yelp public reviews and found dozens of instances where a negative patient review or comment was followed by a response from the respective medical professional.[1]

Don't ever do this! Any public response from you, as the confidential treating physician, violates patient privacy. Multiple court proceedings show that when patient privacy is violated in such a manner, physicians lose out. Negative reviews will occur. Don't react carelessly.

How to engender positive reviews

Although the literature is limited, evidence shows patients are more likely to leave positive reviews if they're content with the physician encounter and outcome.[2,3]

A personable and kind bedside manner, a feeling of having been well treated by office staff, accessible parking and well-kept waiting areas all contribute to the likelihood of a positive patient review. A prompt from the physician or staff is also associated with a higher likelihood of a positive patient review.

On the other hand, the main reason for a negative patient review is any type of miscommunication (which is also the primary reason for medicolegal action). Effective patient communication is critical, from check-in to how the billing department handles benefits.

Other reasons patients leave negative comments include poor bedside manner, abrupt service, unfriendly office staff, long delays and cramped waiting areas.

How to approach negative reviews

So, what's the best way to respond to a negative patient comment or review? First, review the patient experience to ascertain what likely transpired. This will help you and your staff mitigate future occurrences. If you feel the review is fraudulent (e.g., posted by a competitor or personal contact for spite), you can flag and report it.

Second, and I repeat: *Don't reply online!* After reviewing the record, you may feel you are "in the right." Fight the temptation to leave any comment, given the potential for privacy violation and subsequent lawsuits.

Third, fostering good communication with the unhappy patient and resolving the underlying issue is always the best possible outcome. A simple phone call is sometimes all that's needed.

One negative review will not destroy your practice. Don't shy away from online reviews. Continue to ask your patients to rate and review you online because, in most cases, reviews are positive. The overwhelming number of positive reviews will dilute the few negative ones. Having a sign in the office asking patients to leave a positive review is a simple approach that doesn't require any additional face time or staff involvement. A proactive approach for positive reviews may be the best way to deal with negative ones.

REFERENCES

1. Henry TA. How to respond to bad online reviews. American Medical Association. Updated September 2, 2016. https://www.ama-assn.org/delivering-care/patient-support-advocacy/how-respond-bad-online-reviews Accessed March 1, 2019.
2. Sanati-Mehrizy P, Margulies IG, Sayegh F, Ingardiola MJ, Taub PJ. The "RealSelf Effect": Can patient reviews on social media impact clinic volume? Ann Plast Surg. Published online February 27, 2020.
3. Cheshire WP. Autonomic medical practice viewed through the lens of physician-rating websites. Clin Auton Res. Published online January 17, 2020.

Department Editor
David R.P. Almeida, MD, MBA, PhD

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

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

• Twitter: @davidalmeidamd

• Email: drpa@pm.me.

Documentation still counts

In the COVID-19 pandemic, one old rule still applies: If you didn't write it down, you didn't do it.

By Ellen R. Adams, MBA

The COVID-19 pandemic has suspended almost all normal medical operations, both from the practice side and the insurance payer side. Some rules have been waived and special billing codes issued.

The crisis should not, however, cause you to ignore documentation guidelines. You need to continue to document correctly for the level of service you're billing. Avoiding scrutiny and adverse audit findings is important, regardless of external considerations. Though adding stress to your day isn't my intent, it's the wise person who recognizes threats and responds appropriately.

Targeted Probe and Educate

The first level of scrutiny that Medicare uses is called "Targeted Probe and Educate" (TPE). This program uses claims data to identify physician outliers. According to Medicare:

TPE is intended to increase accuracy in very specific areas. MACs [Medicare Administrative Contractors] use data analysis to identify:

- *providers and suppliers who have high claim error rates or* ***unusual billing practices*** *[emphasis added], and*
- *items and services that have high national error rates and are a financial risk to Medicare.*

Providers whose claims are compliant with Medicare policy won't be chosen for TPE.[1]

If you're identified as a TPE target, you'll receive a request from your MAC to submit a sample of 20 to 40 charts for review. If the review finds adequate documentation, the process is closed.

This may happen if a provider is an outlier because of a specialty practice. For instance, a retina surgeon who has few routine new patients will tend to have a higher percentage of complex patients, and thus may bill more Evaluation and Management (E/M) Level 4 and 5 exams, putting the surgeon at risk for TPE evaluation. If those exams are poorly documented, the MAC will start the "educate" process of TPE.

A round of education is followed by a repeat audit. If the documentation has improved, the process ends. If there's no improvement, the MAC can decide to repeat the process or refer the provider for "additional investigation." This may include a fraud or abuse investigation.

Congressional Review

The Comprehensive Error Rate Testing (CERT) process is part of Medicare's required reporting to Congress. Medicare explains the process accordingly:

CMS implemented the CERT Program to measure improper payments in the Medicare FFS Program. Under the CERT Program, a ***random sample of all Medicare FFS claims*** *[emphasis added] are reviewed to determine if they were paid properly under Medicare coverage, coding, and billing rules. Once the CERT Program identifies a claim as part of the sample, it requests via a faxed or mailed letter the associated medical records and other pertinent documentation from the provider or supplier who submitted the claim.*

If there is no response to the request for medical records, the CERT may also make a telephone call to solicit the documentation. Once the documentation is received, it is then examined by medical review professionals to see if the claim was paid or denied appropriately. In this type of audit, the provider receives usually a single page request for one claim. By promptly responding to the record request, the provider will support the claim and usually there is no feedback. It is important to note that CERT data is used

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

Bio

Ms. Adams is a consultant with Corcoran Consulting Group.

She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

Targeting a key GA factor at its source

Investigational treatment FB-L_{RX} targets complement factor B further up the complement cascade.

By Richard Mark Kirkner

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

Ionis Pharmaceuticals describes FB-L_{RX} as a second-plus generation ligand-conjugated antisense drug designed to reduce production of complement factor B (FB), a key protein that has been implicated in a number of complement-mediated diseases, among them dry age-related macular degeneration. FB is produced mostly in the liver and circulates in high levels throughout the vascular system, including the retinal vasculature.

Ionis has partnered with Genentech/Roche to develop the geographic atrophy/dry AMD program for FB-L_{RX}. It's not the only program the two are partnering on. There's a separate program for FB-L_{RX} for immunoglobulin A nephropathy, along with an investigational antisense therapy for Huntington's disease that's in Phase III trials.

At the Angiogenesis, Exudation and Degeneration 2020 meeting in Miami, Sunil Patel, MD, PhD, presented Phase I results of the GOLDEN trial of 52 healthy volunteers exposed to either single or multiple doses of FB-L_{RX} or placebo.[1] The trial reported that the drug produced significant dose-dependent reductions in plasma FB levels along with other key mediators in the systemic complement. Other than moderate adverse events, which were comparable between both the treatment and placebo groups, the study reported no significant safety or tolerability findings.

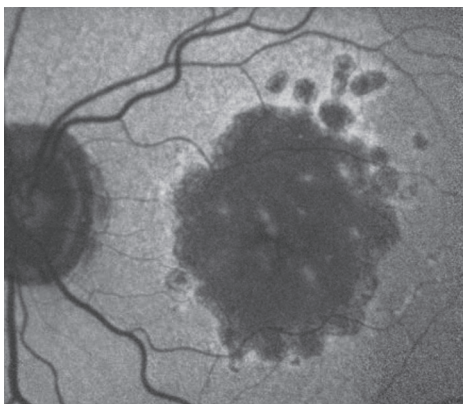

Figure 1. Fundus autofluorescence image of geographic atrophy exhibiting a banded pattern surrounding areas of atrophy, which carries an increased risk of age-related macular degeneration progression. *(Courtesy Nadia Waheed, MD, MPH)*

Now development of FB-L_{RX} is moving into Phase II in patients with GA. Here, David S. Boyer, MD, senior partner with Retina-Vitreous Associates Medical Group in Los Angeles, and an investigator of the trial, answers questions about FB-L_{RX}. Dr. Boyer is a consultant to Genentech/Roche and Apellis Pharmaceuticals.

Q **Describe the mechanism of action in your own words.**

A FB-L_{RX} is an antisense oligonucleotide (ASO). These are short, single-strand DNA molecules that interact with the messenger RNA that prevent translation of a positive gene. In this case, they downregulate the production of FB, which is a novel gene regulator of the alternative complement pathway.

Some genetic-association studies have shown involvement of the alternative complement pathway in GA. By targeting this pathway, the thinking is that the agent won't encounter the interference of the normal complement system. Studies have shown that reducing FB reduces the instance of GA and upregulation of FB appears to increase GA. There's an underlying rationale behind it.

Because most of these factors are produced in the liver, this is where FB-L_{RX} works. It binds to messenger RNA FB, recruiting enzymes to degrade messenger RNA as well as the amount of FB in the systemic circulation.

By targeting the alternative complement pathway, the thinking is that FB-L_{RX} won't encounter the interference of the normal complement system.

Q How does FB-L_{RX} differ from existing therapies?

A The administration is unique; it's subcutaneous. While we've had subcutaneous injections previously, the subcutaneous route has an advantage in that it treats both eyes.

Q Where does the agent fit among the existing approved therapies?

A We don't have a treatment for GA at this moment. Several different modalities are looking at this. Apellis Pharmaceuticals seems furthest along with its complement factor 3 inhibitor (APL-2, pegcetacoplan) enrolling two Phase III trials. The C5 inhibitor avacincaptad pegol (Zimura, Iveric bio) is in a Phase IIb trial. The selective CD inhibitor lampalizumab (Genentech/Roche) failed.

There have been some investigative treatments that target inflammasomes, the inflammatory components of macrophages, to make the readjustment from active to inactive macrophages. However, without having a good animal model, developing a treatment for GA is very difficult. I think that's the reason we're unable to come up with an effective treatment at this time.

Q In addition to safety, what key finding of the Phase I trial will inform the next phase?

A The trial showed a definite reduction in FB levels—a reduction of around 60 percent at 127 days. We know that the effect will probably last for a while, and it will reduce FB plasma levels, and that will reduce FB in the eye.

Q What are the primary and secondary endpoints of the Phase II trial?

A The primary endpoint is to evaluate the change of the area of GA as measured by fundus autofluorescence. The secondary endpoints are FB levels, the effect on low-luminance visual acuity as well as safety and tolerability of chronic administration. Low-luminance VA is becoming more important. Many people with GA have 20/20 vision, but they complain they can't read anything; that they need more light.

Some sites are also using optical coherence tomography to investigate whether the choriocapillaris causes ischemia or becomes thinner during the disease process. RS

REFERENCE

1. Patel SS. Phase 1 results of a systemic antisense inhibitor of complement factor B for geographic atrophy. Paper presented at Angiogenesis, Exudation and Degeneration 2020; Miami, FL; February 8, 2020.

Documentation still counts

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in reporting billing compliance to Congress. ***If a provider ignores a CERT record request, the payment is retracted and the claim is reported as "no documentation"*** *[emphasis added].* *In the congressional report, "no documentation" is not further subdivided and may be interpreted as a fraudulent claim.*[2]

You need to be sure your billing department responds to CERT requests promptly to prevent further scrutiny and having it become part of an accurate congressional report.

Identifying improper payments

Another Medicare audit process is the Recovery Audit Contractor audit (RAC). Medicare's stated goal is:

… to identify improper payments made on claims of health care services provided to Medicare beneficiaries. Improper payments may be overpayments or underpayments. Overpayments can occur when health care providers submit claims that do not meet Medicare's coding or medical necessity policies. Underpayments can occur when health care providers submit claims for a simple procedure but the medical record reveals that a more complicated procedure was actually performed.[3]

This process involves pulling a number of claims and reviewing the documentation for correct coding. If the auditor believes a claim was paid incorrectly, you get an opportunity to defend it in a physician-to-physician telephone call. If the auditor is still unconvinced, your MAC will be alerted with a recommendation to retract payment. You can then appeal directly to your MAC.

A pattern of irregular billing or a whistle-blower complaint could trigger a Medicare audit. If the audit uncovers poor documentation or billing irregularities, you could be charged with fraud or abuse. Serious civil and criminal penalties can follow either charge.

Bottom line: Remain calm

These are extraordinary times, and we're all doing our best to serve patients. However, that is no excuse to ignore your hard-learned lessons in documentation. The basic rule still applies: If you didn't write it down, you didn't do it. RS

REFERENCES

1. Centers for Medicare and Medicaid Services. Targeted Probe & Educate. https://www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/Medicare-FFS-Compliance-Programs/Medical-Review/Targeted-Probe-and-EducateTPE. Updated December 16, 2019. Accessed April 30, 2020.
2. Centers for Medicare and Medicaid Services. Comprehensive Error Testing Rate Fact Sheet: https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/CERTMedRecDoc-FactSheet-ICN909160.pdf. Updated April 2017. Accessed April 30, 2020.
3. Centers for Medicare and Medicaid Services. CMS announces new recovery audit contractors to help identify improper Medicare payments. https://www.cms.gov/newsroom/fact-sheets/cms-announces-new-recovery-audit-contractors-help-identify-improper-medicare-payments. Updated October 6, 2008. Accessed April 30, 2020.

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