My Patient Has Glaucoma... Now What?, *p . 74*

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REFERENCE: 1. Data on file. Bausch & Lomb Incorporated. 3rd Party Industry Report. 2017-2018.

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VOL. 156 NO. 3 ■ MARCH 15, 2019

IN THE NEWS

A new study shows the **risk of cataracts** with too much ultraviolet radiation type B exposure can be **reduced with the topical application of a specific Rho kinase (ROCK) inhibitor**, presently designated Y-27632. Investigators found the responsible transforming growth factor (TGF-β2) could be successfully suppressed by treatment with the ROCK-inhibiting drop. The cataracts are formed when the UVR-B exposure causes TGF-β2 signaling in the lens epithelial cells. The topical ROCK inhibitor, researchers believe, blocks that signal.

Imaizumi T, Kurosaka D, Tanaka U, et al. Topical administration of a ROCK inhibitor prevents anterior subcapsular cataract induced by UV-B irradiation. Exp Eye Res. 2019;181(4):145-9.

A Canada-based research team used whole exome sequencing to identify **two pre-melanosome protein (PMEL) variants associated with heritable pigmentary glaucoma (PG)** as well as pigment dispersion syndrome (PDS)—from which PG stems. Identifying these genes has the potential to be the first step in developing a gene therapy to combat the presently incurable disease.

Lahola-Chomiak A, Footz T, Nguyen-Phuoc K, et al. Non-synonymous variants in premelanosome protein (PMEL) cause ocular pigment dispersion and pigmentary glaucoma. Human Molecular Genetics. December 17, 2018. [Epub ahead of print].

Researchers recently found **micropulse transscleral cyclophotocoagulation**, a noninvasive alternative to glaucoma filtration surgery, **effectively reduces intraocular pressure** (IOP) in keratoplasty eyes. The investigators looked at 61 eyes of 57 patients who received laser treatment and found the procedure reduced IOP by a mean of 35% at 12 months and was well-tolerated by most treated subjects.

Subramaniam K, Price M, Feng M, Price F. Micropulse transscleral cyclophotocoagulation in keratoplasty eyes. Cornea. February 6, 2019. [ePub ahead of print].

Visual Crowding Worse in Glaucoma

Two studies link psychology with physiology.

By Mark De Leon, Associate Editor

Visual crowding occurs when objects that can be recognized in isolation are unrecognizable in clutter. This can limit peripheral vision and explain performance in many daily tasks. A recent study observed pronounced visual crowding in glaucoma patients, even in the presence of only mild visual field loss on standard automated perimetry (SAP). Also, the magnitude of the crowding effect was significantly correlated to the amount of nerve tissue loss as measured by optical coherence tomography (OCT).

In 13 glaucoma patients and 13 controls, researchers measured mean sensitivity with SAP and retinal nerve fiber layer (RNFL) thickness with OCT. To collect visual crowding measurements, participants had to discriminate the orientation of a target letter (T) when presented with surrounding flankers (the letter H) at varying distances from the target. The distance at which flankers degraded the performance in recognizing the target was considered the critical spacing. Glaucomatous eyes had significantly greater (i.e., worse) critical spacing values than controls.

The critical spacing values were significantly associated with RNFL thickness measurements but not with mean sensitivity. The researchers believe this finding suggests that assessing visual crowding may provide a sensitive measure of visual function that corresponds well to the degree of neural tissue loss in glaucoma, even before substantial visual field loss is apparent on SAP.

The researchers also suggest doctors should quantify crowding magnitude in glaucoma patients for tasks that impact safety (e.g., driving) and quality of life (e.g., reading speed). The development and validation of a psychophysical test to quickly assess visual crowding in glaucomatous patients could be a useful tool to assess functional performance in this population.

Ogata NG, Boer ER, Daga FB, et al. Visual crowding in glaucoma. Invest Ophthalmol Vis Sci. 2019;60(2):538-43.

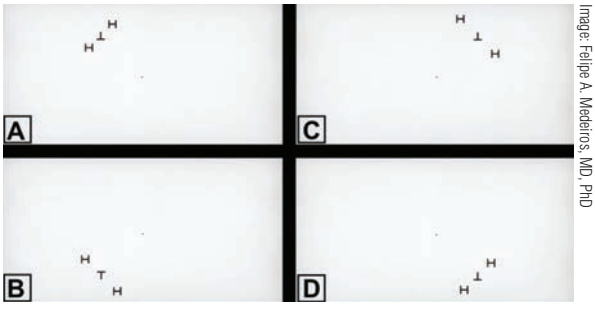

Image: Felipe A. Medeiros, MD, PhD

During the test, subjects fixated on the center dot and identified the T surrounded by the H distractors.

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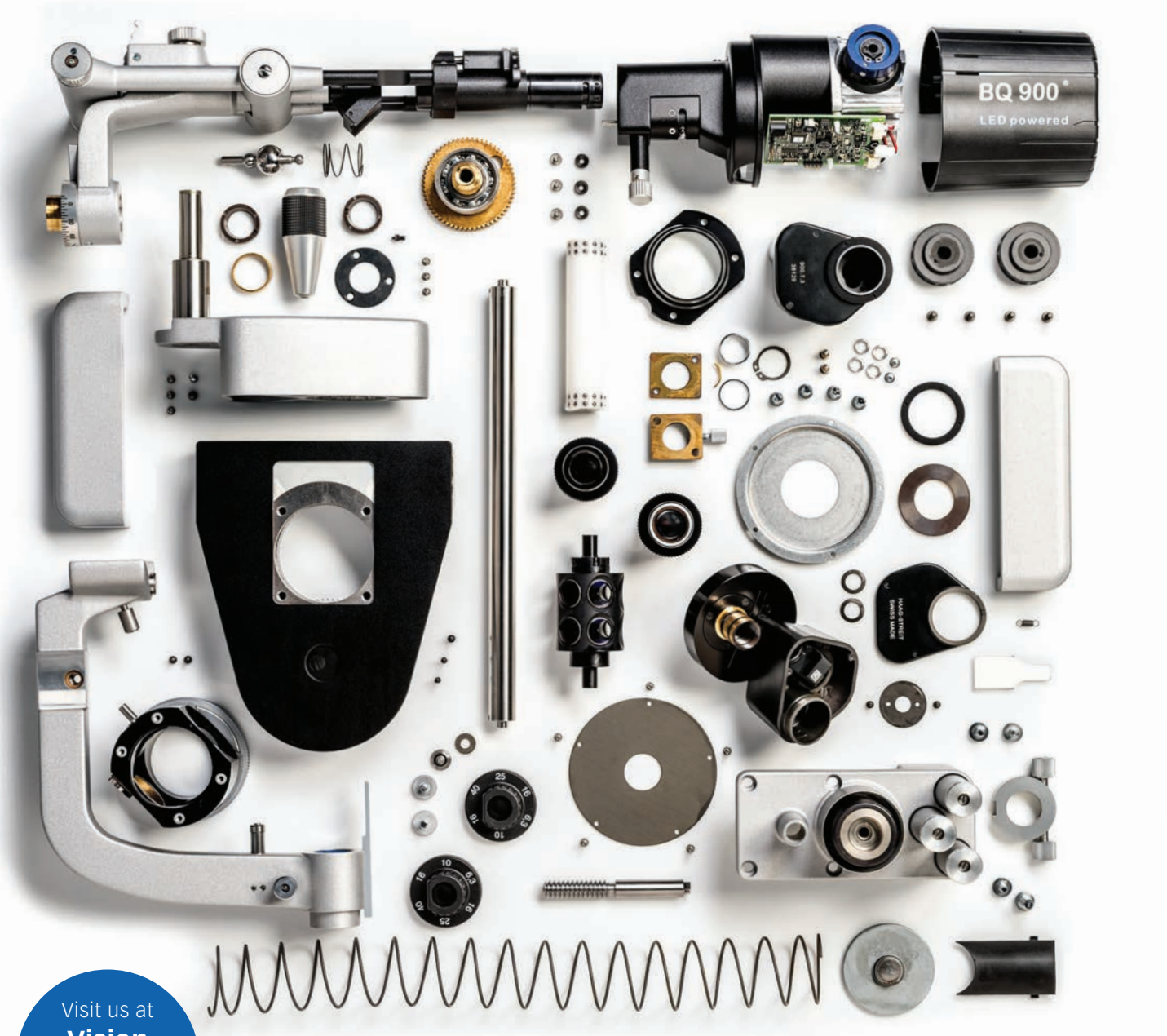

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DED Triples Over Seven-year Period

Dry eye is on the rise no matter your age or gender, according to a new study in *American Journal of Ophthalmology* that found the annual dry eye prevalence rate tripled from 2005 to 2012.

In this large study, researchers analyzed beneficiary medical claims from the Department of Defense Military Health System's military and civilian facilities from 2003 to 2015. Investigators used an algorithm that identified 9.7 million subjects through medical diagnostic codes indicative of dry eye and prescriptions for cyclosporine ophthalmic emulsion. The study looked at overall dry eye prevalence from 2003 to 2015, annual prevalence from 2005 to 2012 and annual incidence rates from 2008 to 2012. They broke the data down by gender, age and ICD-9 diagnostic codes.

Investigators reported overall dry eye prevalence was 5.28%—and more common in women, 7.78% compared with 2.96% in men. The study also found dry eye increased with age (0.20%, 2.03%, 5.74% and 11.66% in subjects aged two to 17, 18 to 39, 40 to 49 and 50 or older, respectively). Within each age group, overall prevalence in women was two to three times higher than their male counterparts, investigators noted.

Photo: Jalaiah Varikooty, Centre for Contact Lens Research

More patients are presenting with positive signs of dry eye than ever before.

Researchers found the annual prevalence rate increased from 0.8% to 3% overall. This included a rise of 1.4% to 4.5% in women and 0.3% to 1.6% in men. Additionally, the annual prevalence rate increased across age groups, starting at 18 to 39 (0.1% to 0.6%) to ages 50 and older (1.8% to 6%).

The study reported the annual incidence rate increased from 0.6% to 0.9% overall. By gender, this rose from 0.8% to 1.2% in women and from 0.3% to 0.6% in men. Across age groups, the annual incidence rate increased starting at ages 18 to 39, (0.2% to 0.3%) to ages 50 and older (1.0% to 1.6%).

"Importantly, data from the present study suggest that annual prevalence and incidence rates have increased over time," the authors wrote. Although the study wasn't designed to identify contributors to this trend, they noted "one likely contributing factor is an increase in education and awareness of DED over time as a treatable condition."

Dana R, Bradley JL, Guerin A, et al. Estimated prevalence and incidence of dry eye disease based on coding analysis of a large, all-age United States health care system. Am J Opthalmol. February 2, 2019. [Epub ahead of print].

Conjunctival Lymphoma: Easy to Miss

Korean researchers recently conducted a retrospective chart review of 199 patients who underwent conjunctival biopsy on suspicion of lymphoproliferative disease. While most patients presented with typical findings, a surprising number had atypical features, the study found.

In total, 261 specimens were studied. The proportion ultimately diagnosed with mucosa-associated lymphoid tissue (MALT) lymphomas was 58.2%. In these patients, the researchers found that the most common slit lamp findings were the "salmon-patch" appearance (73.7%), a follicular distribution (14.5%) and a nodular or subconjunctival mass (6.6%). They note that bilateral manifestations were more common in patients with follicles compared with those presenting with the salmon-patch appearance.

The study concludes that conjunctival MALT lymphoma presents in various ways, so "biopsy should be considered if suspicion is raised, even though the conjunctival lesion does not exhibit the typical appearance of MALT lymphoma." In cases of follicular lesions responding poorly to topical steroids, a conjunctival MALT lymphoma may be suspected, given that chronic inflammation may precede neoplasia in patients with extranodal marginal zone lymphoma.

Jung SK, Paik JS, Park GS, et al. Refractory follicular conjunctival lesions: overlook as just inflammation or not? Br J Ophthalmol. February 1, 2019. [Epub ahead of print].

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ACE Inhibitors Don't Alter Cataract Risk

The link between ACE inhibitor (ACEI) use and cataract development has been a point of debate, but a new study reports this antihypertensive drug is not associated with an altered risk of cataract.

Since some studies found ACEIs were associated with an increased risk of cataract, yet others noted their beneficial effects on cataract development, investigators in this large, case-controlled study assessed the risk of cataract in relation to exposure to ACEIs and other antihypertensive drugs.

Researchers analyzed data from the UK-based Clinical Practice Research Datalink from 1995 to 2015 and included first-time cataract patients aged 40 and older and an equal number of patients without cataracts in the control group. Investigators considered age, gender, general practice, date of first cataract and medical history. Researchers noted the number of ACEI prescriptions, other antihypertensive drugs and the use of single ACEI substances. They performed conditional logistic regression and sensitivity analyses and calculated the risk of cataract associated with previous exposure to ACEIs. Other factors included body mass index, smoking, diabetes, hypertension, prescriptions of systemic corticosteroids and other antihypertensive drugs.

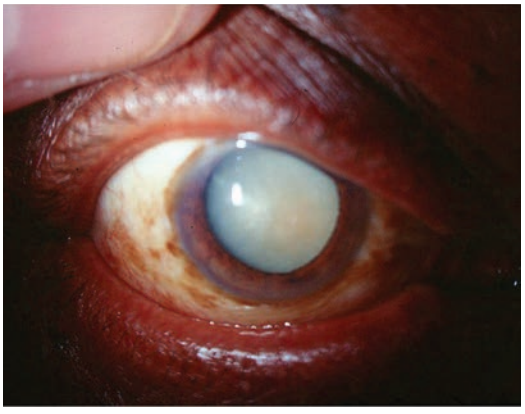

Photo: Alan G. Kabat, OD

A common antihypertensive drug may not contribute to cataract formation after all.

The study identified 206,931 cataract cases and an equal number in the control group. The use of ACEIs was not associated with a materially altered risk of cataract compared with non-use of ACEIs, neither in the main analysis or in any of the sensitivity or stratified analyses, researchers noted. "In our large observational study, use of ACEI was not associated with an altered risk of cataract," investigators wrote in their paper.

Becker C, Jick SS, Meier, CR. ACE inhibitor use and risk of cataract: a case-control analysis. Br J Ophthalmol. February 7, 2019. [Epub ahead of print].

Speaking of Cataracts… Are Pre-op Risk Questionnaires Necessary?

Before undergoing cataract surgery, many patients are issued a preoperative 12-item questionnaire. These are designed to identify patients who are likely to develop postoperative complications. However, a new study published in the *Canadian Journal of Ophthalmology* suggests that they aren't getting the job done. In fact, the University of Manitoba–based research team found no significant difference in the rate of postoperative adverse medical events within 30 days between a group of patients who took the questionnaire and a group who did not. Their research may suggest that omitting the questionnaire altogether could streamline the process.

The researchers looked at two separate groups of patients in Winnipeg who had cataract surgery over two separate six-month periods. A group given the questionnaire experienced postoperative medical events 3.82% of the time, while the group for whom the questionnaire was omitted experienced them 4.12%. Subgroup analyses of major medical events yielded no significant differences between the groups.

In the opinion of the physician chart reviewers, none of the events among low-risk patients in the group who skipped the questionnaire were related to its omission.

Benoit A, Bellan L, Wallace M, et al. Does eliminating the preoperative history and physical make a difference in low-risk cataract surgery patients? A before and after study of 30-day morbidity and mortality. Can J Ophthalmol. February 12, 2019. [Epub ahead of print].

LASIK, SMILE Tied for Outcomes

A recent prospective randomized contralateral eye study of LASIK and SMILE found both procedures led to significant epithelial thickening—with a surprisingly similar response between the techniques, the study says.

Twenty-one patients had LASIK in one eye and SMILE in the other on the same day by the same surgeon. They were followed for two years post-op and evaluated with corneal epithelial mapping using anterior segment OCT.

(continued on page 10)

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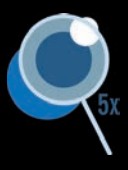

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(continued from page 8)

From a refractive standpoint, the two procedures were not statistically different, given the target of plano: the average uncorrected distance visual acuity for both groups was 0.02 ±0.07 decimal (20/100 Snellen). While this did not come as a surprise, the lack of any statistically significant difference for corneal epithelial thickness was unexpected. Corneal epithelial thicknesses for both groups were statistically significantly different between pre-op measurements and at one, three, six, 12 and 24 months. However, between LASIK and SMILE, the data shows no significant difference.

"These data come as a surprise when considering that LASIK involves a much larger surface intervention than SMILE and intuitively would be suspected to affect epithelial remodeling more," the study authors wrote.

The researchers noted a slight difference in the epithelial thickness variations between LASIK and SMILE; eyes that had LASIK showed greater variation in the minimum and maximum thicknesses compared with SMILE eyes. "Morphologically the epithelium is more homogeneous than in the LASIK group," the study says. "Although not statistically significant, this difference noted may correlate with the milder transient dry eye period noted in the SMILE eyes."

"The data presented herein carry the higher reliability of contralateral eye evaluation that may reduce many of the intersubject bias. Nevertheless, the two procedures seemed to affect epithelium remodeling with more similarity than difference," the study concludes.

Kanellopoulos AJ. Comparison of corneal epithelial remodeling over 2 years in LASIK versus SMILE: a contralateral eye study. Cornea. 2019 Mar;38(3):290-96.

New ROCK Inhibitor for Glaucoma

Clinicians are less than a year into the era of rho-kinase (ROCK) inhibitor use for glaucoma—Aerie's Rhopressa launched in the United States last April—but researchers are already hard at work on additions to this nascent drug class. A recent preclinical study demonstrated the significant IOP-lowering ability of ITRI-E-212 in an ocular hypertensive and normotensive rabbit model. *In vitro* biochemical assays revealed the ROCK inhibitor was highly effective at inhibiting ROCK2 compared with other compounds.

Researchers wanted to create a new amino-isoquinoline ROCK inhibitor compound that would have excellent IOP-lowering effects and corneal penetration, be easily manufactured and cause less conjunctival hyperemia. The most effective compound for lowering IOP was ITRI-E-212, which demonstrated superior inhibitory activity and high relative selectivity for ROCK2.

After administration of 1% ITRI-E-212 eye drops, a maximum IOP reduction of 28.4% was attained at six hours in the ocular hypertensive model; in the normotensive model, a maximum IOP reduction of 25.3% was attained at four hours. The significant difference was not observed until six hours after the administration of 1% ITRI-E-212 in the normotensive and hypertensive groups. Researchers observed only transient, mild hyperemia.

The study concluded that ITRI-E-212 is a novel ROCK inhibitor that may be promising for hindering the progression of glaucoma. ■

Hsu CR, Chen YH, Liu CP, et al. A highly selective rho-kinase inhibitor (ITRI-E-212) potentially treats glaucoma upon topical administration with low incidence of ocular hyperemia. Invest Ophthalmol Vis Sci. 2019;60(2):624-33.

Eye Cream Connected to IOP Rise

Periocular steroid ointment is used for patients with skin issues around the eyes, such as atopic dermatitis or eczema. However, while these medications can address the dermatological issue, they may put some eyes at greater risk, according to a new study published in *Ophthalmic Plastic Reconstructive Surgery*. The New York-based research team found that periocular steroid treatment causes a statistically significant rise in intraocular pressures (IOP) for patients who have an elevated IOP to begin with.[1]

The team looked into the records of 31 patients, 21 of whom were treated bilaterally and 10 unilaterally. They found that eyes with a baseline IOP greater than or equal to 14mm Hg experienced significant pressure increases over the course of a year after only a mean treatment period of 14.2 weeks with topical steroids.[1] Although "this change is not always correlated with a clinically significant rise in IOP, clinicians should monitor more closely patients at greatest risk of steroid response," the report concludes.[1]

Safer options include non-steroidal preparations, such as topical pimecrolimus or tacrolimus, which can be used without limitations.[2]

1. Maeng, M, De Moraes C, Winn B, Dagi L. Effect of topical periocular steroid use on intraocular pressure: a retrospective analysis. Ophthalmic Plast Reconstr Surg. February 4, 2019 [ePub ahead of print]
2. Khan M, Weinberg J. Safe periocular steroid use for eyelid dermatitis. Clinical Advisor. www.clinicaladvisor.com/home/consultations/safe-periocular-steroid-use-for-eyelid-dermatitis. November 12, 2011. Accessed February 26, 2018.

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[1]ASCRS Clinical Survey 2015. Global Trends in Ophthalmology and the American Society of Cataract and Refractive Surgery.

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1 McLaurin E, Cavet ME, Gomes PJ, Ciolino JB. Brimonidine ophthalmic solution 0.025% for reduction of ocular redness: A randomized clinical trial. Optom Vis Sci. 2018;95(3):264-271

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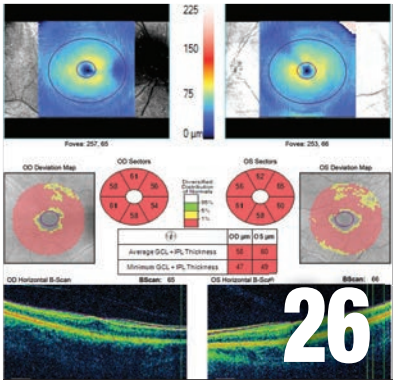

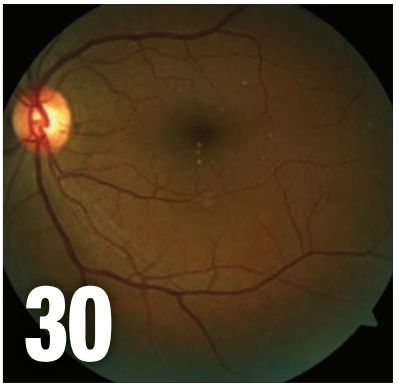

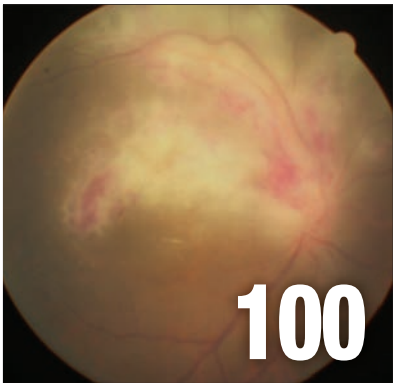

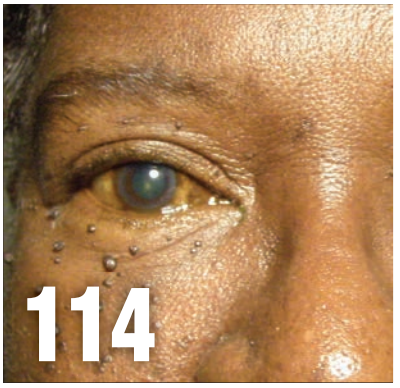

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Outlook

By Jack Persico, Editor-in-Chief

In Between Days

The defeat of the Arkansas expansion bill is more a delay of the inevitable rather than an outright failure.

I started covering optometry way back in 1991. Then, authors had to mail in their articles on floppy discs and we would send them edits on a new high-tech device called a fax machine. That feels like a prehistoric time compared to now. Also, so much has changed clinically since then that it's practically a brand-new profession. But one thing hasn't changed: the way scope of practice expansion efforts play out.

Back in the early 1990s, the drive for TPA laws was still raging. I wrote many news stories that followed a familiar theme. The state optometric association lobbied legislators to allow optometric prescribing rights, citing structural inefficiencies in the system and the subsequent burden placed on patients: delayed care, excessive travel time to ophthalmology offices and disruption of the doctor-patient relationship. Then some MD would fulminate in a newspaper editorial about the imminent harm to patients—from an OD prescribing TobraDex. The state legislators would do some political calculation and then, if the bill failed, everything would start up again the next year. Lather. Rinse. Repeat.

The same pattern played out over and over until we got good or at least decent TPA laws everywhere—except in poor, benighted Massachusetts, where ODs still can't prescribe glaucoma drugs. There's another bill up for consideration in the current legislative session there, of course.

Anyway, when news hit that a recent scope of practice expansion bill failed in Arkansas, the local ODs were right to shrug it off. "We have the utmost confidence for eventual scope expansion in the future," said Belinda Starkey, OD, president of the Arkansas Optometric Association.

The bill would have allowed Arkansas ODs to perform lid lesion removal and minor procedures like SLT. Arkansas, situated between two states that allow laser procedures for optometrists (Oklahoma and Louisiana), does feel like an inevitable win one day. A patient living in a border town could hop in a car, drive west *or* south and be in the chair of an OD with laser privileges within an hour. Why not in-state, too?

That inconsistent access warps delivery of care. For instance, SLT is increasingly being considered early in the course of glaucoma, sometimes even as a first-line therapy. ODs in non-laser states will have to rely more on medication-based regimens, constraining their ability to provide the best care possible, or they'll have to refer to a glaucoma surgeon—inconveniencing and confusing the patient in the process.

Expect these 'lesions and lasers' bills to dominate the scope expansion conversation for the next decade. And we'll see both sides run the same legislative playbook from the DPA and TPA eras, with results much the same. Success for optometry in every statehouse isn't guaranteed, but the forthcoming battles will be more tedious than tense. Many wins are just a matter of time.

Eventually, once the stakeholders make peace with optometric primary eye care, this *Groundhog Day* loop will finally end and everyone, MDs included, will be better off. ■

Vyzulta® as First-line Treatment for Patients with Open-angle Glaucoma and Ocular Hypertension

Alexander Kabiri, OD

The initial standard treatment for patients with open-angle glaucoma (OAG) is medical by tradition. Topical prostaglandin analogs (PGAs) are the most frequently prescribed first-line eye drops for lowering intraocular pressure (IOP),[1] thanks to their tolerability and proven efficacy in lowering IOP. Other classes of topical IOP-lowering medications, including beta blockers, alpha agonists, and carbonic anhydrase inhibitors (CAIs), are commonly used as second-line therapy.[1] Vyzulta® (latanoprostene bunod ophthalmic solution) 0.024% is novel among PGAs in its chemical structure. Upon topical ocular administration, Vyzulta is metabolized into two moieties: the first, latanoprost acid, is a prostaglandin F2 analog; while the second, butanediol mononitrate, releases nitric oxide (NO). Vyzulta is thought to lower IOP by increasing aqueous humor outflow through both the uveoscleral and trabecular routes. Having demonstrated sustained IOP-lowering efficacy and an acceptable safety profile in clinical studies, Vyzulta is a first-line treatment of choice for the medical management of glaucoma patients.

Glaucoma is a family of multifactorial optic neuropathies, which, if left untreated, may cause irreversible optic nerve injury and vision loss. Elevated IOP is a major risk factor for glaucoma progression that can be modified with treatment.[2-7] Thus, IOP reduction remains the cornerstone of treatment for all patients with glaucoma and ocular hypertension.

Normal healthy eyes maintain IOP by balancing aqueous humor production with outflow from the anterior chamber, which occurs via two main routes—uveoscleral (IOP-independent) and trabecular (IOP-dependent) outflow pathways.[8] The trabecular pathway is the primary or "conventional" route of aqueous outflow and a key site of pressure regulation in the human eye.[9] NO, a signaling molecule produced by endothelial cells in Schlemm's canal, promotes aqueous outflow through the trabecular pathway.[10-13] It does so by activating the NO-soluble guanylate cyclase–cyclic guanosine-3',5'-monophosphate (NO-sGC-cGMP) signaling pathway, inducing cellular and meshwork relaxation, and opening pores in the trabecular meshwork (TM).[13-15]

In patients with primary open-angle glaucoma (POAG) or ocular hypertension, TM responsiveness is thought to be compromised and outflow resistance increased due to cellular stiffness from chronic cellular contraction, protein deposition (eg, cochlin), and/or glycosaminoglycan-related edema within TM and Schlemm's canal tissues.[8,9] Evidence of reduced NO markers in the anterior chambers of eyes with POAG further supports the use of an NO-releasing molecule to lower IOP.[16-18]

INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin F2 analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

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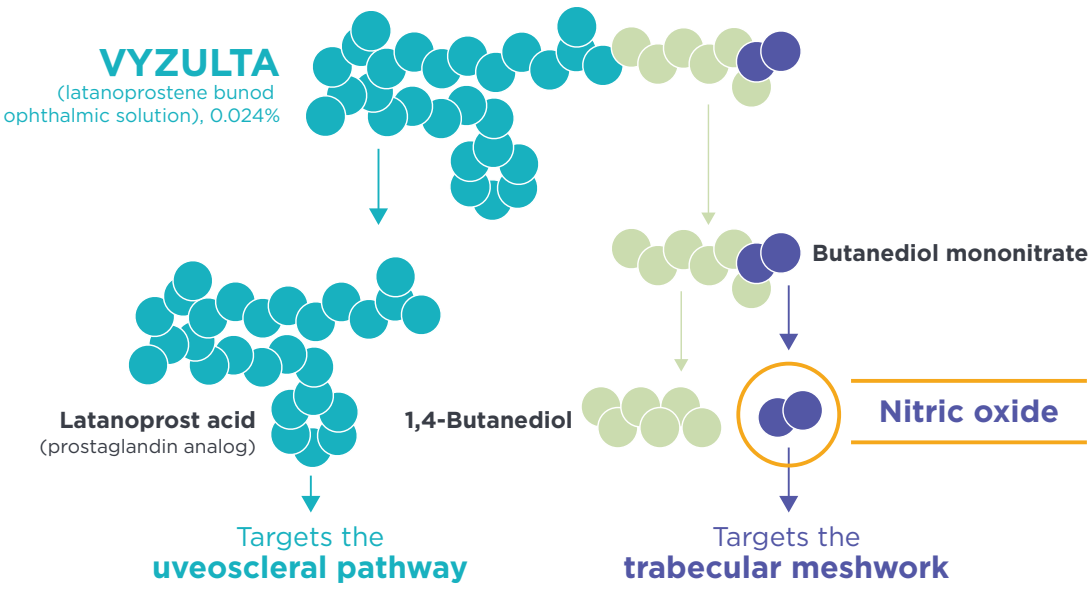

FIGURE 1

One molecule, two pathways: Vyzulta® (latanoprostene bunod ophthalmic solution 0.024%) is a nitric oxide-releasing prostaglandin F2 analog that increases both trabecular and uveoscleral outflow.

Standard First-line Therapy

Current options for the treatment of glaucoma include PGAs, beta blockers, CAIs, and alpha agonists.[19] As a class, PGAs work by increasing aqueous humor outflow via the uveoscleral pathway;[20] due to their superior IOP-lowering efficacy,[21-26] safety, tolerability, and convenient once-daily dosing, PGAs are commonly prescribed first line.

Despite multiple drug choices, however, many glaucoma patients do not reach target IOP with a single-agent regimen.[19] Even if pressure is maintained within target levels, some patients may continue to develop progressive glaucomatous damage and visual field loss. These treatment challenges highlight a continued need for additional effective therapies and strategic use of current agents.

Targeting Two Pathways

Vyzulta (latanoprostene bunod ophthalmic solution), 0.024%, an NO-releasing prostaglandin F2 analog indicated for the reduction of IOP in patients with OAG or ocular hypertension, enhances both trabecular and uveoscleral aqueous outflow.[27-28] Vyzulta is metabolized into two moieties—latanoprost and butanediol mononitrate, which releases NO—creating a dual-acting agent.[28] (Figure 1).

The release of NO by Vyzulta is important, as evidence suggests that abnormal NO formation or signaling may play a role in glaucoma pathology.[16] NO is synthesized by nitric oxide synthase (NOS) in endothelial cells at various sites in the body, inducing vasodilation, gastric emptying, and other dilatory or relaxation-inducing functions.[16,18] In normal eyes, Schlemm's canal cells modulate NO synthesis to maintain homeostatic control of IOP.[28] NO is a gas and cannot be directly measured due to a half-life of mere seconds;[16] however, reduced aqueous humor concentrations of NO markers (eg, cGMP, NADPH, and total nitrite levels) in glaucomatous eyes supports the hypothesis that low NO levels contribute to increased IOP.[16-18]

When instilled in the eye, Vyzulta is rapidly metabolized to latanoprost acid, a PGA, and butanediol mononitrate, which releases NO; both moieties are active and responsible for the molecule's pharmacological activities.[28] While latanoprost acid increases uveoscleral outflow, the release of NO leads to a cascade of cellular events that culminates in increased outflow at the TM. After diffusing into TM cells, NO activates the sGC/cGMP/protein kinase G pathway, thus indirectly inhibiting rho kinase and calcium channels.[28]

Vyzulta in Clinical Trials

In clinical studies of up to 12 months' duration in patients with OAG or ocular hypertension, the IOP-lowering effect of Vyzulta dosed once daily was up to 9.1 mm Hg from baseline.[25-27] In VOYAGER, a phase 2, 29-day dose-ranging comparison study of subjects with OAG or ocular hypertension, Vyzulta (n = 83) led to a 9 mm Hg decrease from baseline—an additional IOP reduction of 1.23 mm Hg over latanoprost 0.005% ($P = 0.005$; n = 82).[29] Vyzulta had an acceptable safety profile.[29]

The two pivotal phase 3 clinical trials—APOLLO and LUNAR—evaluated the noninferiority of Vyzulta vs. timolol 0.5% in patients with OAG or ocular hypertension. In LUNAR (N = 420), IOP

TABLE 1

Vyzulta: Superior IOP Reduction for All Timepoints at Month 3 vs. Timolol (*P*=0.006)

APOLLO

Month 3	Vyzulta: mm Hg IOP at timepoints	Vyzulta: Reduction from baseline mm Hg	Timolol 0.5%: mm Hg IOP at timepoints	Timolol 0.5%: Reduction from baseline mm Hg
BASELINE	26.7	—	26.5	—
8 AM	18.7	-8	19.7	-6.8
12 PM	17.9	-8.8	19.2	-7.3
4 PM	17.8	-8.9	19.2	-7.3

LUNAR

Month 3	Vyzulta: mm Hg IOP at timepoints	Vyzulta: Reduction from baseline mm Hg	Timolol 0.5%: mm Hg IOP at timepoints	Timolol 0.5%: Reduction from baseline mm Hg
BASELINE	26.6	—	26.4	—
8 AM	18.7	-7.9	19.6	-6.8
12 PM	17.9	-8.7	19.2	-7.4
4 PM	17.7	-8.9	19.1	-7.3

Superior IOP reduction for all time points at month 3

APOLLO and LUNAR were phase 3, randomized, multicenter, double-masked, parallel-group studies comparing the safety and efficacy of Vyzulta with timolol 0.5% in subjects with open-angle glaucoma or ocular hypertension. The primary objective of these two studies was to demonstrate that the mean IOP reduction after 3 months of treatment with Vyzulta QD was noninferior to timolol 0.5% BID. Superiority was a secondary endpoint of these trials.

reduction with Vyzulta dosed once daily at night was noninferior to that with timolol 0.5% dosed twice daily. In APOLLO (N = 420), IOP reduction with Vyzulta dosed once daily at night was superior to timolol 0.5% dosed twice daily at month 3.[25,26] In APOLLO and LUNAR, Vyzulta achieved superior IOP reduction for all time points at month 3 vs. timolol; superiority was a secondary endpoint of these trials (Table 1). The most common ocular adverse reactions observed in patients treated with Vyzulta were conjunctival hyperemia (5.8%), eye irritation (4.3%), eye pain (3.1%), and instillation site pain (2.1%).[27]

In the JUPITER study, a phase 3 single-arm, multicenter, open-label clinical trial, Vyzulta produced a statistically significant, stable IOP reduction over a 1-year treatment period in Japanese patients (N = 130) with predominantly normotensive OAG. Mean baseline IOP was 19.6 mm Hg in study eyes, and 75% of patients had IOP between 15 and 21 mm Hg.[30] The mean IOP in study eyes was reduced from 19.6 mm Hg at baseline to 14.4 mm Hg at week 52—a 26.3% IOP reduction ($P < 0.001$).[30]

Role in Clinical Practice

When treating new patients, the goal is to achieve target IOP in order to slow or stop disease progression and help preserve good vision. Research has shown that for every 1 mm Hg IOP reduction, risk for disease progression is reduced by 10% to 19%.[2-3,31] Vyzulta showed statistically significantly greater mean IOP reduction than latanoprost;[29] this factors into my decision-making when prescribing treatments for new and established patients. I am also encouraged by a low dropout rate in clinical trials: 0.6% of Vyzulta-treated subjects in the APOLLO and LUNAR studies discontinued due to an ocular adverse event.[30]

As it has been shown to be effective at reducing IOP, Vyzulta has the potential to replace the current PGAs as a first-line drug for patients with OAG or ocular hypertension. Since the development of Vyzulta, gone are the days when I felt the only conceivably beneficial switch for patients who were not responding to their current therapy was a switch from one PGA to another. I can now choose to substitute Vyzulta, which is one molecule with two mechanisms of action, for the primary PGA.

When counseling patients about Vyzulta, I explain that it is dosed once-daily in the evening and review potential side effects, including pigmentary changes, lash growth, redness, irritation, and pain. We advise patients regarding proper drop technique and to avoid allowing the tip of the dispensing container to touch the eye or fingers to prevent contamination.[27]

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Conclusion

In summary, patients with glaucoma have evidence of less endogenous NO than patients without glaucoma. Vyzulta lowers IOP through latanoprost acid, which increases uveoscleral aqueous outflow, and the release of NO, which is thought to increase conventional outflow.[28] The latter mechanism is novel among PGA agents—and direct since the TM is the main site of outflow obstruction in glaucoma.[28] Given its IOP-lowering effects, Vyzulta is a treatment on the leading edge of medical management of glaucoma and ocular hypertension.

Dr. Alexander Kabiri

Alexander Kabiri, OD, is a comprehensive optometrist in private practice in New York City and adjunct clinical professor at SUNY College of Optometry. Dr. Kabiri's areas of expertise include dry eye disease, allergic disorders, glaucoma and ocular hypertension, post-operative inflammation, corneal disease, point-of-care testing, and practice management. Dr. Kabiri is a paid consultant to Bausch + Lomb.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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New Meds: Today and Tomorrow

Our pharmaceutical toolbox is practically bursting at the seams these days.

By Paul M. Karpecki, OD, Chief Clinical Editor

Today's ODs have a robust armamentarium for treating just about anything that walks through the door, from the ubiquitous red eye to more nuanced conditions such as dry eye and glaucoma. Here's a preview of what's coming.

Dry Eye Pipeline

In addition to the usual suspects, clinicians can now consider Klarity-C (Imprimis), a compounded ophthalmic emulsion that contains cyclosporine 0.1% and chondroitin sulfate. Cequa (Sun Pharmaceuticals), which is cyclosporine 0.09% combined with a nanomicellular matrix vehicle to aid in drug penetration, should be available later this year.

These are all in Phase III FDA clinical trials: OCU-310 (Ocugen), CyclASol (Novaliq), T-1580 (Thea), RGN-250 (RegeneRx), Visomitin (Mitotech) and Moisview eye drops (HU-007, Huons).

Other promising drugs in Phase II trials: ADX 102 (Aldeyra); Cambium (Elate Ocular), an autologous serum–derived drop; Novaliq's NOV03, which contains perfluorohexyloctane; the nasal spray OC-02 (Oyster Point); voclosporin (Aurinia); Lubris (Novartis), a protein-based product; the neurotrophic peptide BRM 421 (Brim Biotechnology); TOP1630 (TopiVert), a kinase inhibitor; and SHP-659 (formerly P-321, Shire), an epithelial sodium channel inhibitor.

The list for early-phase clinical trials is even more significant, and I look forward to sharing insights as their clinical results progress.

New Target for Glaucoma

The most exciting development for glaucoma is our ability to treat the trabecular meshwork (TM). The nitric oxide (NO) in Vyzulta (Bausch + Lomb) targets the TM but also affects the blood vessels, allowing for greater outflow. Rhopressa (Aerie) is a rho-kinase inhibitor that expands the TM. In 2019 we may see Rocklatan (Aerie), a Rhopressa/latanoprost combination that shows significant intraocular pressure (IOP)-lowering effects. Sun Pharmaceutical's Xelpros, another recent approval, is BAK-free and is ideal for glaucoma patients with ocular surface disease.

As for compounding options, Imprimis is a nationwide provider of Simple Drops. The quad formulation is timolol 0.5%/brimonidine 0.15%/dorzolamide 2%/latanoprost .005% in a single preservative-free (PF) 5ml bottle. The triple drop of timolol 0.5%/brimonidine 0.15%/dorzolamide 2% comes in PF 10ml bottles. I recently prescribed triple and quad Simple Drops for a patient who was confused by his dosing and was struggling to reach his target IOP of 16mm Hg. The different bottle sizes help because he takes the triple drop (larger bottle) in the morning and the quad drop in the evening. His pressures are now consistently at 12mm Hg and 13mm Hg.

Retina Therapies

New anti-VEGF therapies may soon join Lucentis (Genentech), Eylea (Regeneron) and off-label Avastin (Genentech), according to retina specialist John Kitchens, MD. Brolucizumab (Novartis) should gain approval this year. This small molecule acts similarly to other therapies but has a higher molar equivalent and a greater binding affinity. Abicipar (Allergan), which may come in 2020, has similar durability to brolucizumab. Genentech has a Phase III trial of a port-delivery system that may reduce injection frequency and a bi-specific molecule targeting both VEGF and ANG-2.

Red Eye Relief

For years we've been telling patients to avoid vasoconstrictor drops—and with good reason. Drops that use oxymetazoline and naphazoline hydrochloride, primarily alpha-1 receptor agonists, affect the arterioles and constrict the eye's oxygen supply, causing ischemia. The body's response is vasodilation and tachyphylaxis, leading to overuse and potential corneal toxicity. They also have significant systemic side effects. Thus, patients who want a redness remover should use an alpha-2 receptor agonist such as Lumify (brimonidine 0.025%, Bausch + Lomb). Alpha-2 receptor agonists primarily constrict the venules, which removes the risk of ischemia.

We've never had so many new options in so a short time, and we must stay on top of the latest advancements to better manage our patients' ocular conditions. ■

Note: Dr. Karpecki consults for a number of manufacturers with products relevant to this topic.

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Let the Truth Set You Free

Quit worrying about number one or number two. We have bigger truths to face, like that golf shirt you are wearing. **By Montgomery Vickers, OD**

Truth is one of those things they often refer to as an "absolute." There's no in between and it's either a fact or it's not. Which is true? Number one or number two?

Hmmm, that sounds right. We refract in search of the truth, or at least something that makes the patient see better.

The Truth is Murky

But if it's that simple, why do patients pick number one and later return wanting number two? It's because truth is not always absolute. At one point in history, the truth was that the world was flat. Later, that was disproven, and it was believed that the world was round and the sun rotated around us, which is oddly not the truth. That led to astronomy, the loss of Pluto as a real planet (it's now a dwarf planet, as we all know) and finally the physics of light, which led to us learning how to adjust glasses in school.

The truth set optometrists free to wear golf shirts on Fridays and to join the right country club. Amazing what getting rid of a flat earth can accomplish, unless you are a member of the Flat Earth Society or you accept crappy vision plans.

Yes, there are still people who believe that the earth is flat. They also believe you can put a multifocal contact lens on someone and they can clearly see distance and near with no concerns. They all work in the marketing department for multifocal contact lens companies.

Truths ODs Live By

But despite the "truth" that there actually may not be such a thing as truth other than as a fundamental quality of the Great Creator, we have to hang our hat on something. Maybe instead of truth we should be talking about what we truly believe.

I believe that:

1. The most important thing I can do is not be the stupidest employee. This has led to some interesting hires along the way, because sometimes it's hard to avoid being the stupidest employee. My employees often prove I actually AM the stupidest employee sometimes.
2. If you smile you can almost say anything to a patient and they will still like you. *Almost* is the salient word here, so don't push your luck unless you first refer to #1 above.
3. A patient actually wants the doctor to examine them and not via video chat from the golf course. Am I naïve?
4. Every time a patient calls you on Saturday, his eye was injured last Wednesday.
5. Not every patient really cares if they can see.
6. Every time a newborn baby cries, he's sitting on the lap of my next patient.
7. There is something bigger than "I cannot see through my new contact lenses." For example, "I also cannot see through my new glasses."
8. Worrying about your practice won't make it better, but adding cannabidiol oil to your patient's water bottle might.
9. No doctor should ever worship money unless, of course, you have bills to pay.
10. Your brothers and sisters should get the best eye care that money can buy; therefore, they should go see somebody who actually makes them pay for stuff.

The truth will set you free! Any day now…

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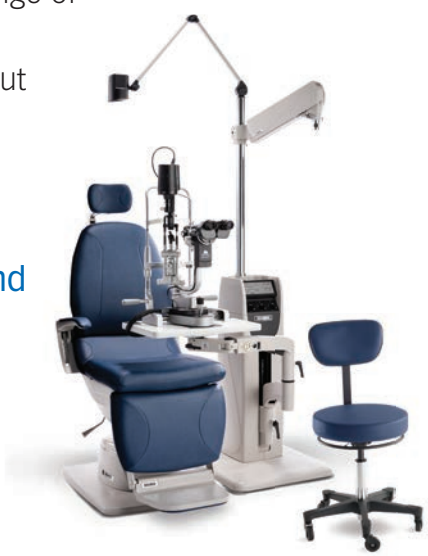

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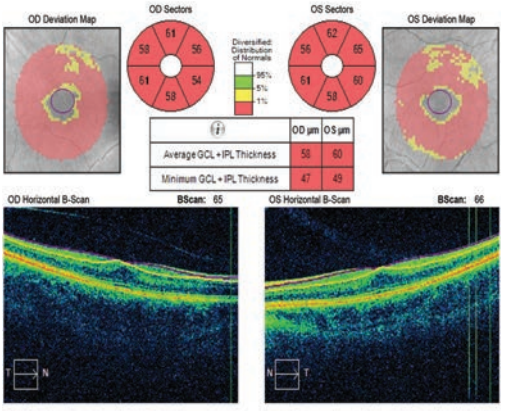
Don't Bet on Red

Know how to use OCT data to decide whether a patient truly has glaucoma.

Edited by Paul C. Ajamian, OD

Q I have a new spectral-domain optical coherence tomographer (SD-OCT) that I used to perform an optic nerve evaluation on a patient. The test shows a very thin nerve fiber layer (NFL) and ganglion cell layer thinning. The patient has para-nasal visual field defects in both eyes. Her discs look normal, her IOP is 15mm HG OU and there is no family history of glaucoma. Is this low-tension glaucoma?



Ganglion cell analysis revealed a reverse foveal pit and no vitreal macular traction.

A Brian Den Beste, OD, of LP Eye Consultants in Orlando, had the same thing happen to him recently. A 47-year-old Caucasian female came to his practice. He examined the patient and confirmed the OCT and visual field findings that the referring optometrist found. The patient's history revealed that she has been on blood pressure meds for the past eight years, and she admitted to never having perfect vision. Her glasses revealed a low hyperope prescription, with 20/25 vision OU.

Her pachymetry measurements were normal at 520mm. Her fundus exam revealed healthy optic nerves with 0.3 central cups and no visible optic nerve drusen. The average retinal NFLs showed symmetry but were both thin at 66µm. The macular ganglion cell complex (GCC) was also extremely thin with an average thickness of 60µm. The Matrix visual field was also reviewed and showed nasal loss OU.

The horizontal B-scan showed a "reverse divot" OU, without vitreal macular traction but with a "bump" instead of a depression. This correlated with the patient's history of long standing vision less than 20/20.

Dr. Den Beste says this finding is not uncommon in patients who are referred to him as glaucoma suspects. "It's easy to throw out GCC and NFL data when there is macular traction and the tissue is obviously distorted," he adds. "It is more difficult when there are subtle changes that don't seem to make sense."

OCT Assurance

While optic nerve drusen or tilted disc syndrome can cause unusual NFL findings and nasal field loss, the patient didn't have evidence of that. Optic nerve hypoplasia is also in the differential when the discs are less than 1.5mm. Dr. Den Beste's patient had normal disc diameters. A prior history of optic neuritis would obviously affect both the ganglion cells and the overall nerve fiber thickness but often is accompanied by disc pallor.

Similar findings are present with compressive lesions in the visual pathway. Diabetic retinopathy can also greatly affect OCT data. None of these associated findings were pertinent in this case.

"We see a lot of patients who are referred as glaucoma suspects with asymmetric cupping or bilateral large cups, and the OCT is a great tool to rule in or out glaucoma," Dr. Den Beste says.

Many of these individuals who have asymmetric cups also have asymmetric discs, so the "disc area" is the first item he looks at when evaluating the OCT print out. "It's easy with funduscopy to note a difference in cup size but not so easy to assess disc size," he says.

This patient was relieved to know she didn't have a progressive disease, like primary open-angle glaucoma, but she is due to have a repeat OCT and visual field exam in six months to make sure her findings are not progressive. The beauty of an objective test like OCT is that it is repeatable, and Dr. Den Beste is predicting that the results won't change.

The chief lesson here: don't just look at the color key with OCT. "Seeing red" may lead you to an incorrect diagnosis. Look at other findings to be sure that your patient really has glaucoma. "The OCT B-scan images will assist your diagnostic decisions," says Dr. Den Beste. "They help delineate ganglion cell damage from a macular etiology as opposed to an optic nerve etiology." ■

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RPE: The Multitasking Master

This simple structure is crucial for maintaining visual function in more ways than one.

By Bisant A. Labib, OD

The retinal pigmented epithelium (RPE) is composed of a hexagonal monolayer of epithelial cells. Despite its structural simplicity, the RPE plays an essential role in many cellular processes necessary for visual function.[1,2] Both the RPE's location within the retina and its cellular characteristics directly correlate with its functions, and a breakdown of these processes is implicated in many retinal diseases.[1]

Anatomical Overview

The RPE is located between the photoreceptor (PR) layer of the outer retina and Bruch's membrane.[1,2] In the macula, the cell size and shape of the RPE appear flatter and shorter than in the periphery. The apical surfaces of RPE cells contain microvilli that aid in transepithelial transport and the absorption of nutrients from the surrounding extracellular milieu.

The lateral surfaces of the cells are bound together through tight junctions, which are integral, considering the RPE is part of the blood-retinal barrier.[1-3] RPE cells are also coupled through gap junctions in other areas, allowing for the diffusion of gases and nutrients across the choroid to the PR. This facilitates the oxygen supply for PR function and aids in the transport and storage of retinoids necessary to maintain the visual cycle.

Composition

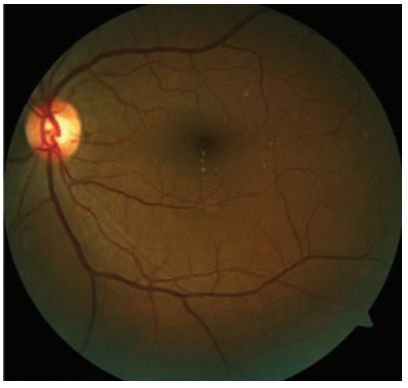
The "pigment" of the RPE is due to high amounts of melanin granules with greatest density in the posterior pole and macular region, giving rise to the darker coloration on fundus examination.[1] The melanin's primary function is to provide a barrier against reflected light that would otherwise degrade vision.[3] There are also phagosomes, lysosomal enzymes and receptor molecules tasked with the signaling of phagocytosis of primarily rod outer segments, which is necessary for the visual cycle. This metabolic activity is higher in the macula, as is the ratio of PR cells per RPE.[1]

The RPE is in frequent exposure to visible light for absorption and is more susceptible to reactive oxygen species formation and oxidative damage.[1,2] To counterbalance this, the RPE contains antioxidants—a protective measure that declines with age and disease processes.[1] Finally, the immunosuppressive factors housed in the RPE contribute to the eye's immune privilege.[2]

When Disease Strikes

Disruptions in RPE structure and function result in many retinal diseases. A disturbance of RPE melanin during development results in ocular or oculo-cutaneous albinism. In the aging eye, material may deposit between the RPE and Bruch's membrane, known as drusen.[3]

More importantly, the RPE is implicated in age-related macular degeneration (AMD).[4] In the early, non-exudative form, oxidative stress and inflammation leads to diminished RPE function and degradation, causing drusen and RPE cell death.[5,6]



Drusen deposits in the RPE are a harbinger of retinal disease such as AMD.

The RPE is also involved in diabetic retinopathy, as prolonged hyperglycemia impedes nutrient and water transport across the RPE. Hyperglycemia is also associated with the reduction of antioxidant activity in the RPE, leading to higher levels of cell damage.[2]

Understanding how this simple layer works diligently to maintain the processes necessary for visual function is essential because any disruption through disease and aging can compromise retinal integrity. ■

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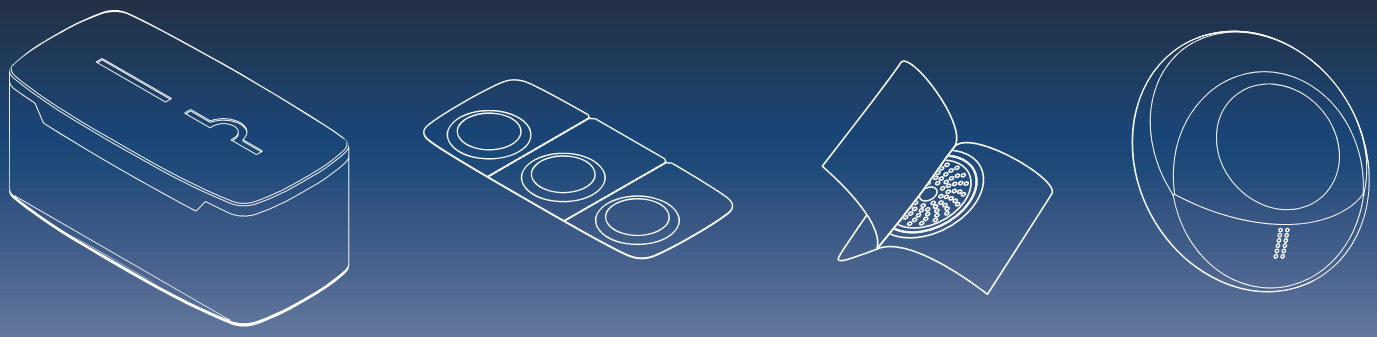

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Glaucoma Tools: Know the New Codes

Increased use of new diagnostic technology led to changes that impact your workup.

By John Rumpakis, OD, MBA, Clinical Coding Editor

Diagnostic testing for glaucoma suspects never seems to stagnate. Significant changes that apply to recent technologies became effective on January 1, and they may affect how you approach your glaucoma workup.

Declaratory Statements

First, I am not a glaucoma specialist and rely on both the American Optometric Association (AOA) Clinical Practice Guidelines and the American Academy of Ophthalmology (AAO) Preferred Practice Patterns when discussing recommended tests.[1,2]

Second, third-party carriers only pay for testing that is medically necessary for a patient based on their clinical presentation. Therefore, panel testing (i.e., running the same battery of tests on every patient indiscriminately based on a specific diagnosis) is not appropriate.

Potential Confusion

The latest changes that may affect your clinical decision making have to do with adjunctive testing for glaucoma suspects. Both the AOA and AAO agree that in addition to the physical examination itself, supplementary testing can include:[1,2]

1. Visual fields (9208X)
2. Fundus photography (92250)
3. OCT of the optic nerve (92133)
4. Gonioscopy (92020)

This differs significantly from what is typically discussed in continuing education forums today. Other tests, such as visual evoked potential (VEP), electroretinogram (ERG) and corneal hysteresis, conducted and billed for on a standard basis may or may not be appropriate. The recent upswing in the use of these tests for diagnosing "glaucoma suspects" has led to major changes in their coding.

The first change came in 2018 for VEP. Because many were using the 95930 code to test for glaucoma suspects, the AMA removed glaucoma from the CPT definition:

- 95930: VEP checkerboard or flash testing, central nervous system except glaucoma, with interpretation and report.[3]

The Category III code, 0464T, was added specifically for use with a glaucoma suspect:

- 0464T: VEP, testing for glaucoma, with interpretation and report.[3]

Changing from a Category I to a Category III code also shifts the payment responsibility to the patient.

In 2019, ERG is receiving a similar treatment with the removal of 92275 and the addition of:[3]

- 92273: ERG with interpretation and report; full field (i.e., ffERG, flash ERG, Ganzfeld ERG).
- 92274: ERG with interpretation and report; multifocal.
- 0509T: ERG with interpretation and report, pattern (pERG).

As with VEP coding, the pERG code, which was typically used for a glaucoma suspect, has been moved to a Category III status, essentially putting it into a patient pay status.

Corneal hysteresis, another test gaining in popularity, has the accompanying code:

- 92145: Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral, with interpretation and report.[3]

While not a new code, it has no current formal policy of coverage set by any Medicare carrier.

Practice Pearls

- Panel testing is not a sound approach, unless you are billing the third-party carrier only for the tests for which you have clearly established medical necessity.
- Insurance carriers do not pay for preventive medical testing you do to eliminate or reduce your medical liability.
- A pattern is emerging where frequently done tests are being re-categorized in the CPT as Category III, which defines them as new or emerging technology. This often shifts the financial responsibility of the test to the patient.

Our mission is to provide comprehensive eyecare responsibly, ethically and at a level commensurate with each patient's clinical presentation. The changes occurring within the CPT are numerous but ones we are bound to follow. Adhering to the rules helps you provide the individualized care patients deserve and protects you and your practice. ■

Send questions and comments to rocodingconnection@gmail.com.

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3. www.CodeSAFEPLUS.com. Accessed January 29, 2019.

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How Macular Carotenoids Optimize Patient Care

In a Q&A session, Professor John Nolan discusses the latest evidenced-based research revealing the importance of prescribing macular supplements to patients.

John Nolan, PhD,
is director of the Nutrition Research Centre Ireland; principal investigator, Macular Pigment Research Group, Waterford Institute of Technology; and Howard Chair; European Research Council Fellow; Fulbright Scholar.

1. How can macular supplements benefit patients in the eye care practice from a protective standpoint?

Over the last two decades, we have learned about the possibility of using nutritional supplements to reduce the risk of age-related macular degeneration (AMD). Such a possibility is extremely important for eyecare, given the aging and growing population—and subsequent increases in AMD cases. In the US alone, more than 2 million people over the age of 50 have late AMD and 11 million people have some form of AMD.[1,2] The idea that nutritional intervention could reduce risk of AMD was fueled by the original AREDS trial,[3] which demonstrated a major (25%) risk reduction of AMD progression from intermediate to advanced AMD. However, since this trial was published in 2001, science and technology has progressed at an exceptional rate, and researchers have been able to identify the exact nutritional molecules that have been proven to reduce the risk of AMD and improve visual function, across all populations.[4,5] These nutritional molecules are known as the macular carotenoids or macular

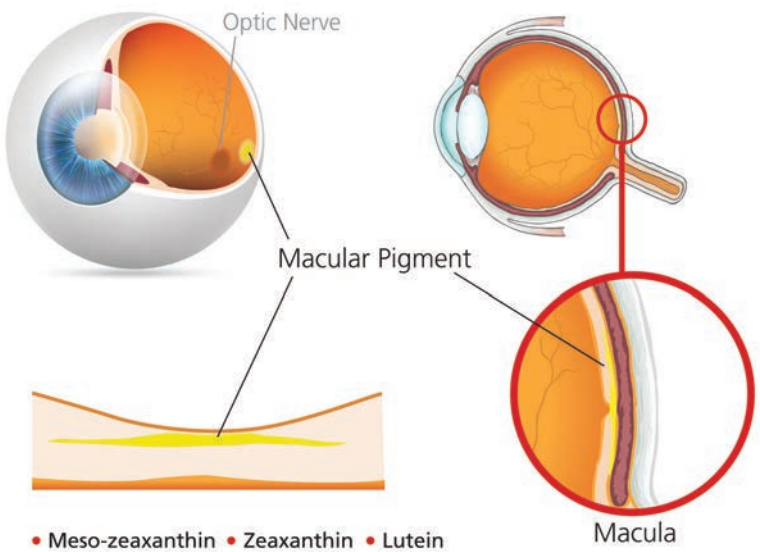

Image: John Nolan, PhD

The Macula & Macular Pigment. Macular pigment (MP)—which gives the macula its yellow color—is a term used to describe a collection of three dietary carotenoids located at the macula. These carotenoids—lutein, zeaxanthin and meso-zeaxanthin—are found in equal concentrations at the macula, with meso-zeaxanthin serving as the dominant carotenoid at the center of the macula.

pigment (meso-zeaxanthin, lutein and zeaxanthin).

Remarkably, these molecules are found in equal concentrations at the macula, and studies have demonstrated the importance of supplementation with all three carotenoids.[4-8] The macula is the central 4% of the retina that mediates central and color vision. For optometrists, this evidence-based science represents a truly unique opportunity to not just reduce patients' risk of AMD, but to actually enhance visual function in healthy patients.[4] The internal optics of the eye are optimized by enriching macular pigment, as the macula benefits by filtration of short-wavelength (blue) light by the yellow-filtering pigment. The health of the macula is also enhanced as a result of the antioxidant and anti-inflammatory properties of macular pigment. For the optometry practice, it is also important to utilize new technologies that allow for sensitive assessment of visual function and risk of retinal diseases. Data shows that successful implementation of these novel technologies greatly improves patient care and practice outputs.

2. Are there any findings to support the role of macular supplements in supporting or even optimizing patient vision and visual performance?

Yes, this is a very important question. We must not just consider nutritional intervention as something we should do when patients develop AMD. Remember, it is the antioxidant and light-filtering properties of macular pigment that enhance the health and optics of the macula, respectively; and this is important ever before AMD presents. The opportunity, therefore, is for all of our patients. This pigment is in the macula for visual function. When a mother breastfeeds, she provides the macular carotenoids to her baby. Nature does not do this to protect against a disease that presents in our sixties!

A number of key studies support the importance of macular pigment in maintaining or enhancing visual abilities that are important for visual performance. Research from the Nutrition Research Centre Ireland, Waterford Institute of Technology demonstrated that a daily nutritional supplement containing lutein, zeaxanthin and meso-zeaxanthin improved the visual performance of people with normal visual acuity and free of retinal pathology (CREST Normal Trial).[4] In the one-year study, 53 adult subjects took a daily supplement containing 10 mg lutein, 2 mg zeaxanthin and 10 mg meso-zeaxanthin (commercially known as MacuHealth). Their visual performance outcomes were compared with those of 52 age-matched controls who took a placebo supplement for the same period. At the end of the 12 months, participants who had taken the carotenoid supplement showed significant improvement in contrast sensitivity. This improvement correlated with increased levels of macular pigment measured in the eyes after nutritional supplementation. It is important to note that contrast sensitivity correlates highly with subjective visual performance, and therefore is a very good measure of visual function.[9]

In a separate trial known as CREST AMD[5] (again with the 10:10:2 carotenoid formula plus the AREDS co-antioxidants—commercially known as MacuHealth Plus) over a 24-month intervention period, patients with the early stage of AMD exhibited clinically meaningful improvements in contrast sensitivity at the end of the study. This is a very important discovery because patients with early AMD typically experience a decrease in visual function; however, these findings identified a way to improve visual function in these patients.

3. What is the danger of not encouraging patients to supplement with macular nutrients such as lutein, zeaxanthin and meso-zeaxanthin in light of increasing use of digital devices and exposure to damaging blue light?

I would go as far to say that eye care professionals must not just encourage patients to supplement with the macular carotenoids, but they must prescribe these supplements. Eye care should be driven by evidenced-based science and medicine. The evidence is now overwhelmingly directing us to fortify the retina with these key micronutrients. The yellow macular pigment is ideally located, and has the ability to neutralize free radicals and optimize the use of light and protect against damaging blue light. This is now more important than ever because we are living longer and exposed to significantly more blue light than ever before. Failure of the optometrist to implement macular pigment nutritional strategy in the clinic represents a danger and failure to the patient.

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Dry Eye Drugs: New Approaches to an Old Problem

Its multifactoral and variable nature makes DED a challenging condition to manage. These novel therapeutics are here to help. **By Chandra Mickles, OD, MS**

Patients presenting with ocular burning, stinging and sometimes painful symptoms of dry eye disease (DED) are becoming more common in today's optometric practice. More than 16 million Americans are coping with this disease, which can have a significant impact on quality of life.[1-3] In addition, DED is a growing problem for both mature patients and young adults.[1,3]

Although DED is widely encountered in eye care practices, the number of pharmaceutical agents available to combat it pales in comparison with other chronic diseases.[1-3] Fortunately, new and upcoming dry eye medications may change the landscape of DED management for the better. Here is a comprehensive look at new dry eye drugs and a preview of treatment options of the future.

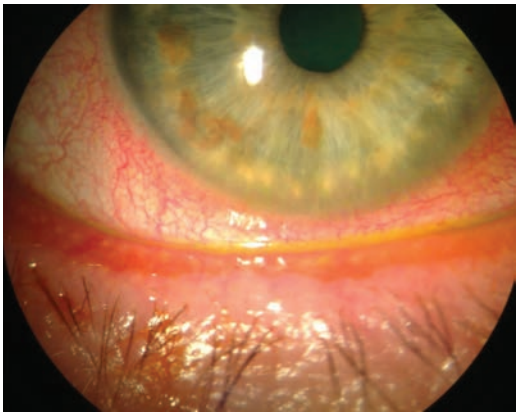

Fig. 1. Conjunctival hyperemia is an excellent marker of ocular surface inflammation. A new topical steroid may help reduce this DED sign.

Primary Target: Inflammation

Several new therapeutic options are tackling this age-old problem associated with DED:

Cyclosporine (CsA). The last decade has seen a tremendous growth in our understanding of the pathophysiology of DED, and treatment options have shifted from solely artificial tear supplementation to disrupting the underlying disease processes such as inflammation.[4] Many new and future dry eye drugs target the cycle of inflammation on the ocular surface that perpetuates this disease.[5]

Recently, Cequa (CsA ophthalmic solution 0.09%, Sun Pharma) joined Restasis (CsA 0.05% ophthalmic emulsion, Allergan), an immunomodulatory agent, and Xiidra (lifitegrast ophthalmic solution 5%, Takeda-Shire), an LFA-1 antagonist, as the third DED prescription drug approved by the FDA in 15 years. Like Restasis, Cequa is indicated for the treatment of keratoconjunctivitis sicca with the familiar BID dosage and supplied in single-use vials.[6]

Cequa is a first-in-class topical formulation with the highest FDA-approved concentration of cyclosporine

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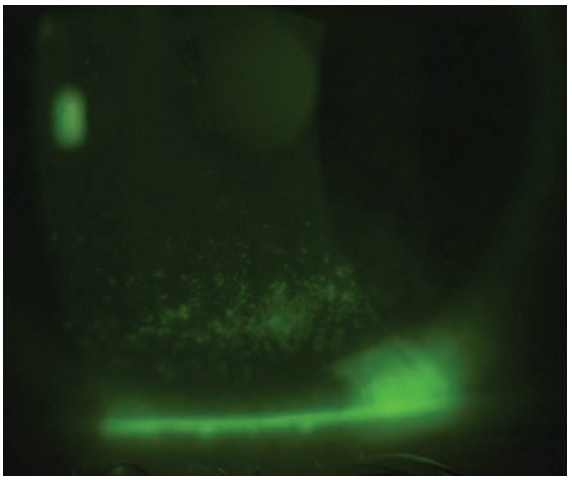
and a novel nanomiceller technology, which overcomes the longstanding challenges of cyclosporine's delivery to ocular surface tissues.[6] The high hydrophobicity of the lipophilic CsA impedes the drug's ability to penetrate the aqueous layer.[6,7] Cequa's nanomiceller formulation overcomes this barrier by forming small micelles or aggregates of amphiphilic molecules where the water-loving polar heads form an outer shell that faces the aqueous, while the non-polar, water-hating tails are sequestered inward to form a hydrophobic core.[6]



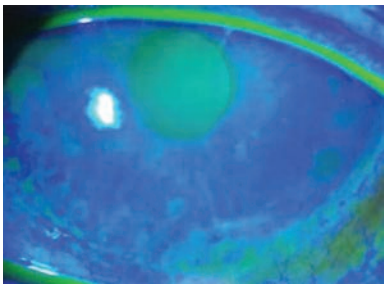


Fig. 2. Moderate-to-severe ocular staining is best managed with anti-inflammatories. Artificial tears with lubricants with anti-inflammatory-containing properties such as trehalose could be beneficial in these cases.

Through this delivery system, high concentrations of CsA can penetrate the ocular surface tissues and potentially provide better patient outcomes. Evidence suggests that improvements in signs and symptoms are seen earlier with Cequa than with other cyclosporine formulations available in the United States.

In a Phase III trial of Cequa, there were statistically significant improvements in Schirmer's score at three months and ocular surface staining at one month.[6] These improvements are earlier than the six months until improvement in Schirmer's tear strip wetting and corneal staining seen with the lower concentration cyclosporine, Restasis, and earlier than the three month improvement in corneal staining seen with Xiidra.[8,9] While a promising new drug, one medication won't work for everyone, especially for a heterogeneous condition such as DED.

Although the reported mild to moderate adverse reactions of these DED medications are similar, responses to a drug, whether suboptimal or optimal, depend on the individual.[6]

Klarity-C (cyclosporine/chondroitin sulfate 0.1% ophthalmic emulsion, Imprimis Pharmaceuticals) is a new compounded non-preserved topical BID eye drop used for DED management. It combines the active ingredient CsA 0.1% with lubricants in a chondroitin sulfate emulsion. Its unique benefits are the higher concentration of cyclosporine and the chondroitin sulfate vehicle. Chondroitin sulfate is a lubricant that also has mild anti-inflammatory properties and can minimize instillation irritation, which is a common patient concern.[10,11] Both Klarity-C and Restasis increase tear production and improve tear film instability and ocular surface staining, although Restasis has a better impact on goblet cell density.[11]

Ikervis (CsA 0.1%, Santen) and CyclASol (CsA 0.1%, Novaliq) may be future cyclosporine options in the United States. Ikervis, available in Europe, is a once-daily preservative-free formulation.[12] It is a cationic emulsion containing CsA that leads to the long-lasting presence of CsA in the tear film and a higher bioavailability than the anionic CsA formulation of Restasis.[12,13] As a result, with only once-daily dosing, Ikervis is well tolerated and significantly improves symptoms and signs of patients with severe DED by six months.[12,14]

CyclASol is a promising cyclosporine that uses a non-aqueous perfluorobutylpentane technology based on semifluorinated alkanes. This formulation may improve bioavailability of CsA and onset of efficacy. In a Phase II study, CyclASol showed a significant reduction in corneal and conjunctival staining compared with both the vehicle and Restasis with an onset of effect at two weeks.[7]

These formulation breakthroughs, in conjunction with the invalidation of patents for Restasis, have opened the door for more, and even generic, CsA options.

Corticosteroids. Soft topical steroids are valuable for dry eye management, especially in acute flare-ups that necessitate rapid relief. However, the potential side effects of elevated intraocular pressure (IOP) and cataracts limit their use. KPI-121 (0.25% loteprednol etabonate ophthalmic suspension, Kala Pharmaceuticals) could be the first FDA-approved product for the short-term, two-week treatment of DED.

KPI-121 uses a mucus-penetrating particle drug delivery system to enhance penetration of this familiar steroid into ocular tissues.[15] Thus far, two Phase III trials show mixed results regarding ocular discomfort. One shows

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statistically significant improvement in ocular discomfort, while the other does not demonstrate a significant improvement.[15] Both studies show a consistent statistically significant reduction in conjunctival hyperemia, with IOP elevations similar to the placebo (*Figure 1*).[15,16] The results of the third Phase III trial investigating the temporary relief of signs and symptoms of DED with KPI-121 are expected some time in the fourth quarter of 2019.[15]

Thymosin β-4. RGN-259 (Thymosin β-4, RegeneRx Biopharmaceuticals) promotes ocular surface healing by stimulating corneal epithelial cell migration and decreasing inflammatory cytokines.[17] In a study investigating the effects of RGN-259 topical treatment on DED in a mouse model, 10 days of treatment with RGN-259 led to the recovery of mucins and goblet

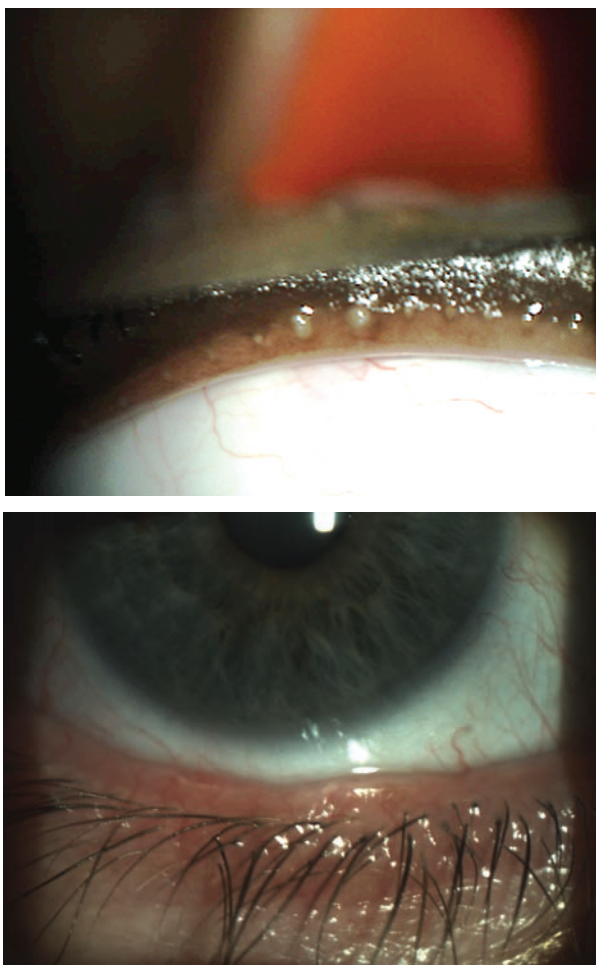


Fig. 3. Patients with MGD-associated DED may soon have a new therapy option with NovaTears, a 100% perfluorohexyloctane lubricant that is a water- and preservative-free lipophilic liquid.

cells, improved corneal integrity, increased tear production and reduced inflammation.[18] The investigators suggested that RGN-259 was comparable with or even better than Xiidra in improving the functions of the cornea, conjunctiva and lacrimal glands of mice.[18] Thus far, Phase II trials show positive results for improving symptoms and signs of DED and demonstrate a strong safety profile with fewer side effects compared with products currently on the market.[19]

Brimonidine tartrate. More commonly known for its IOP-lowering effect, this also has anti-inflammatory properties.[20,21] Ocugen is working toward FDA approval of a twice-daily preservative-free drop of 0.2% brimonidine ophthalmic solution for the treatment of DED called Ocu310. It is a nanoparticle formulation of 0.2% brimonidine designed to increase the drug's efficacy by prolonging retention time on the ocular surface.[22] Data from recent Phase III clinical trials is expected in the second half of 2019.[22]

Unconventional Targets

With the growing need for dry eye therapeutics, pharmaceutical companies are looking at several novel targets for dry eye relief, many of which are making their way through the FDA approval process:

Mucin secretogogues. Mucins play a vital role in stabilizing the tear film and helping the tear film adhere to the ocular surface. Tavilermide (MIM-D3 ophthalmic solution, Mitogen Pharmaceuticals/Allergan) is a peptidomimetic that stimulates mucin-like production by activating mitogen-activated protein kinase systems involved with mucin production, which can also potentially aid in corneal healing.[23] In clinical trials, this topical medication improved symptoms and signs of DED in 28 days and had a favorable safety profile.[23] Thus far, the drug seems promising.

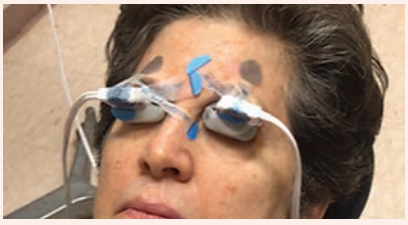
Diquafosol ophthalmic solution 3% (Santen) and rebamipide 2% ophthalmic solution (Otsuka) are two other drugs that promote mucin secretion and, although both are available in Asia, further clinical trials in the United States have been terminated because they failed to meet clinical endpoints.[24-28]

Sodium channel blockers. SHP-659 (formerly P-321, Takeda-Shire) is a Phase II investigational topical drug that may address DED by blocking ocular surface epithelium sodium channels. These play a key role in regulating the hydration of the ocular surface by controlling the reabsorption of tears through transport of sodium and water.[29,30] As an epithelium sodium channel inhibitor, SHP-659 inhibits the absorption of sodium and water, thereby maintaining ocular surface hydration.[30]

The Dry Eye Device Boom

While the proliferation of dry eye pharmaceutical agents has been sluggish, the dry eye device market has not. Optometrists have several effective instruments to manage their patients. Two recent device additions that have created a buzz are Allergan's TruTear intranasal tear neurostimulator and Alcon's iLux. TruTear is a handheld, patient administered intranasal neurostimulating device. The disposable tips are inserted into the nasal cavity to induce the production of natural tears through gentle neurostimulation of the trigeminal nerve, which innervates the goblets cells and both the lacrimal and meibomian glands.[1] As a result, the device can potentially produce tears containing aqueous, lipids and mucin. Recent studies demonstrate that the device not only improves DED symptoms but can also cause a significant increase in tear volume with total lipid and protein concentrations equivalent to basal tears.[2-4]

iLux is also a handheld portable device with a disposable tip. However, this in-office instrument is primarily used to treat MGD-associated DED. A practitioner can treat MGD by using LED light energy to heat the inner and outer eyelids via disposable pads. While applying heat and manually controlled expression, the practitioner can view the eyelid margin with a magnifying lens to tailor the treatment for each individual. iLux treatment has produced clinically and statistically significant improvements in the symptoms and signs of MGD.[5] A new comparison study demonstrated that iLux is equal in efficacy and tolerability to Lipiflow (Johnson & Johnson Vision).[5]



While Lipiflow is a first-of-its-kind device to treat MGD-associated DED, several new treatment approaches are on the way that also hold promise for providing relief.

NuLids (NuSight Medical) is a new doctor-prescribed, home-use dry eye device that treats MGD. Analogous to an electric toothbrush, the electric "lid brush" is used for 60 seconds per day to remove collarettes and decap blocked meibomian glands.[6] A company-sponsored study found it improved dry eye symptoms and signs, as well as meibomian gland function.[6]

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In animal models, SHP-659 increased tear volume and was well tolerated in a study of dry eye patients.[29,30] Future clinical trials should provide more information about its efficacy.

Lacrimal glands. Lacriprep (lacritin, TearSolutions) is another promising topical DED medication curently in clinical trials. It is a fragment of the lacritin protein, which is a glycoprotein released from the lacrimal glands. Research shows reduced levels of this protein are associated with dry eye signs.[31-33] Lacritin can promote basal tearing in eyes of rabbits and rescue cultured human corneal epithelial cells from inflammatory cytokine stress in dry eye patients.[33] A Phase II clinical trial of patients with Sjögren's-associated DED is underway.[34]

Reducing dry eye symptoms and signs may be yet another application for Botox (botulinum toxin type-A, Allergan). While intraglandular injection of Botox is off-label, injection into the lacrimal gland and near the punctum can reduce lacrimal and tear drainage, respectively.[35] In a study of intractable DED patients, Botox injection into the medial part of the eyelid improved symptoms and signs and reduced tear cytokine levels.[36]

Trigeminal nerve. OC-02 (Oyster Point Pharma) is a nasal spray of a nicotinic acetylcholine receptor agonist that stimulates the trigeminal nerve to increase natural tear production.[37] In Phase II trials, tear production and symptoms improved significantly.[37]

Artificial Tears

Not long ago, DED was solely treated with artificial tears, which provided only temporary relief. Fortunately, we now have drugs that address the disease process of DED. Nonetheless, artificial tears remain an excellent economical first step or a complementary therapeutic. New formulations that offer more than simple tear supplementation may change the playing field for the artificial tear market:

Trehalose. This disaccharide with high water retention capabilities is naturally found in plants and animals and is both a bioprotectant and an osmoprotectant.[38,39] It protects corneal cells from the harmful effects of desiccation and tear hyperosmolarity—a hallmark of DED—by fortifying cell membranes and preventing the denaturation of proteins in the absence of water.[4,38,39]

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Research shows trehalose-containing artificial tears improve DED symptoms and signs, including the suppression of inflammation (*Figure 2*).[40,41] Recently, three trehalose-containing artificial tears, Theratears Extra (Akorn), Refresh Optive Mega-3 (Allergan) and Thealoz Duo (Théa), entered the market with the potential to benefit DED patients beyond lubrication.

Perfluorohexyloctane. NovaTears (Novaliq) is a one-component eye drop containing 100% perfluorohexyloctane. This unique lubricant is a water- and preservative-free lipophilic liquid. NovaTears stabilizes the lipid layer and can improve signs of meibomian gland dysfunction (MGD), as well as symptoms and signs of DED (*Figure 3*).[42-44] NovaTears is currently available in Europe and Australia in multidose bottles and is in Phase II clinical trials in the United States.[45]

As this once unappreciated condition garners more attention, the number of promising candidate therapies that should bring dry eye relief grows. They may one day overcome some of the frustrations clinicians face with today's management strategies. ■

Dr. Mickles is an associate professor and the coordinator of the Dry Eye Care Center at Nova Southeastern University College of Optometry. She is a fellow of the American Academy of Optometry and the Scleral Lens Education Society. She lectures and publishes in the areas of ocular surface disease and contact lenses. She is also a principal investigator of dry eye and contact lens research investigations.

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PEER • REVIEWED • PRA • ARTICLE

The Changing Landscape of Glaucoma Therapy

The future looks promising with the recent introduction of new treatment options.

By Greg Caldwell, OD, Tracy Offerdahl, PharmD, and Joseph Sowka, OD

When evaluating options for glaucoma management, the number of treatments is growing and changing at a pace that is faster than ever. Historically, optometrists have had a relatively limited number of choices for their glaucoma patients, not only in terms of topical medications but also surgical interventions. There are changes on the horizon, as, now more than ever, practitioners have a fairly large number of topical medications in their arsenal, with even more on the way.

Vyzulta, Xelpros and Rhopressa offer great change for glaucoma therapy.

Non-pharmacologic procedures and surgeries have been discovered or refined, including a newer generation of minimally invasive glaucoma surgery (MIGS), laser procedures and surgical techniques, such as modified goniotomy and other angle surgeries.[1,2] This article will focus on the topical treatment options for glaucoma and highlight newly marketed topical agents, as well as treatments that are currently in clinical trials. Additionally, we will discuss the impact of generic formulations.

Growing the Market

The FDA approved a new set of topical glaucoma medication approvals in 2017 and 2018. This had a significant impact on optometric practice, as it had been 23 years since a new medication category (prostaglandin analogs) or a new mechanism of action (increase in uveoscleral outflow) had been approved for the management of ocular hypertension and glaucoma.

What makes these approvals even more exciting is that they are agents with novel mechanisms of action. So, as this "drug drought" is ending, the optometric community is starting to see how exciting and impactful these new approvals are going to be.

In 2017, the FDA approved Rhopressa (netarsudil ophthalmic solution 0.02%, Aerie) and Vyzulta (latanoprostene bunod ophthalmic solution 0.024%, Bausch + Lomb).[3,4] In 2018, the FDA approved Xelpros (latanoprost ophthalmic solution 0.005%, Sun Pharma).[5] These changes to the topical glaucoma drug world mark a defined shift not only in terms of new pharmaceutical agents

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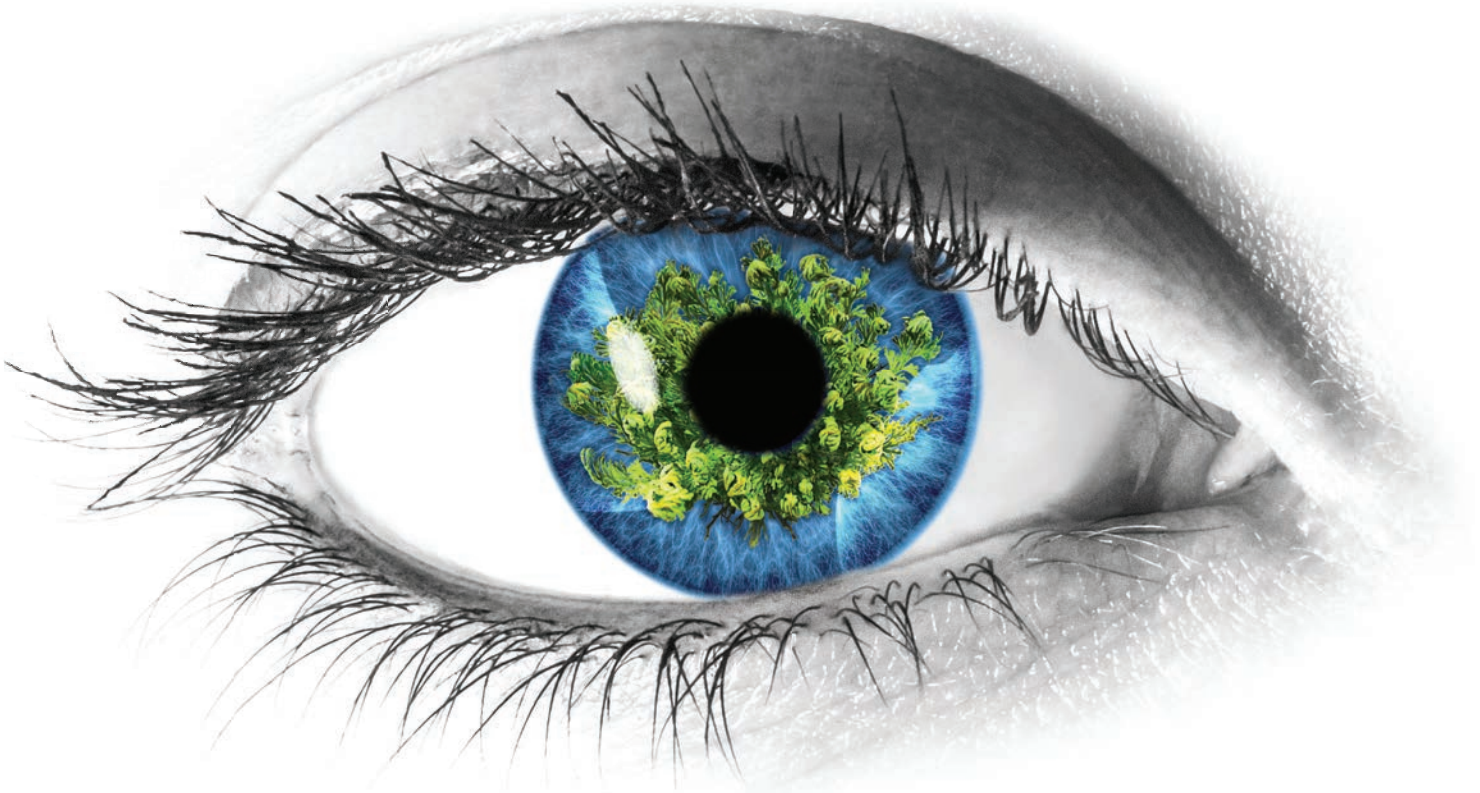

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but also in who is bringing these treatments to market. With Aerie Pharmaceuticals, Bausch + Lomb and Sun Pharmaceuticals in the glaucoma arena, our drug arsenal has grown substantially.

Generics and Prescribing

Choosing the best medication for a patient with glaucoma (or any diagnosis) is not as simple as it sounds. Clinical education and training doesn't prepare us for that dreaded call from the pharmacist or patient who was just told: "That drug is not covered by insurance," or, "Prior authorization needed for that drug." Even more common is, "Insurance requires use the generic version." While those phone calls can be a nuisance, some may actually impact the quality of a patient's care. Despite the best efforts of the FDA regarding the manufacturing of generic drugs, evidence suggests that topical ophthalmic medication and their "generic equivalents" are not always exactly equivalent.[6-8]

It is true, however, that the generic equivalent to a branded agent must have the same active ingredient, the same strength/concentration and use the same dosage form and route of administration.[9-11] However, bioequivalence studies are not required, and that may be one of the biggest potential problems associated with this "generic equivalent" mindset that insurance companies seem to mandate.[6-8]

Furthermore, gone are the days of simply writing a prescription for an anti-glaucoma medication and sending it to a local retail pharmacy or a 90-day mail order pharmacy to be filled. It also seems that we are at an all-time high where clinicians need prior authorization or a coupon card in order to prescribe a branded glaucoma product cost-effectively. These cumbersome and time-consuming steps have led some manufacturers to develop the "direct pay" method. Xelpros and Sun Pharmaceuticals follow this method, as it offers the optometrist and the patient no prior authorizations, no coupon or coupon activation, no callbacks and prompt product fulfillment and refills. Sun Pharmaceuticals calls it "Xelpros Xpress" and is using Capstan and Transition as their partner pharmacies.[12]

Direct pay is now available to all patients, regardless of insurance coverage. Contracts between preferred pharmacies and pharmaceutical companies that supply medication allows medications to be sold at a set agreed-upon price. In other words, negotiation can now be between a drug manufacturer and the pharmacy rather than with managed care insurers.

This bypasses insurance benefits, and the patient is charged the set price regardless of coverage. Optometrists can also electronically prescribe or fax the prescription directly to a preferred pharmacy. Once received, the pharmacy contacts the patient to confirm mailing address and to establish a payment method. The medication is subsequently mailed to the patient, who also has the option for enrolling in an auto-refill program.

Compounding pharmacies, such as ImprimisRx, are limited to dispensing for home use.

Compounded Drugs

The expiration of patents and the subsequent development of numerous generic glaucoma therapies has led to compounding pharmacies to formulate "poly-generic" medications (i.e., products that contain multiple active ingredients). These companies target patients who need several different drugs in their therapeutic regimens.

Regulators have begun putting greater scrutiny on compounding pharmacies following incidents linked to poor oversight by state boards of pharmacy. The FDA has divided compounding pharmacies into two sectors: 503A and 503B.[9] The FDA has designated 503A compounding pharmacies as those that compound according to prescriptions specific to particular patients and are required by state boards of pharmacy to comply with USP and other guidelines.[9] These facilities are limited to dispensing only for home use and are not allowed to compound large batches.

The FDA has designated 503B compounding pharmacies as those with outsourcing facilities that may manufacture large batches with or without prescriptions to be sold to healthcare facilities for office use

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only.[9] These pharmacies are allowed to use larger batches to lower their manufacturing costs, therefore passing the savings onto consumers. ImprimisRx is a 503A and 503B compound pharmacy providing glaucoma preparations as a 503A compounding pharmacy.[13]

The availability of numerous generic medications has allowed poly-generic therapy to evolve with two to four medications being placed into single bottles for patient convenience. To be sure, all medications used have been proven to reduce intraocular pressure (IOP) in clinical trials. There is, however, very limited information regarding how well these poly-generic medications work, particularly when compared with their single-ingredient equivalents. Going forward, this is surely an area of important comparison and study.[9-11]

Topical Newcomers

Vyzulta was FDA approved in November 2017. It is indicated for the once-daily management for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Vyzulta's mechanism of action works in two ways: It uses the uveoscleral pathway to increase aqueous humor outflow, and uses butanediol mononitrate to release nitric oxide (NO), which increases outflow through the trabecular meshwork and Schlemm's canal.[14]

The well-known prostaglandin analog side effects were reported and no new adverse events surfaced because of the butanediol mononitrate and release of nitric oxide. Reported ocular adverse events were similar to other prostaglandin analogs and included conjunctival hyperemia, eye irritation, eye pain and instillation site pain, increased pigmentation of the iris and periorbital tissue and growth of eyelashes.[14]

When Rhopressa was approved in December 2017, it broke the 23-year drought in the topical ophthalmic drug world, where no new or novel mechanisms of action were introduced. It is indicated for the treatment of glaucoma or ocular hypertension, which gives practitioners the ability to start treatment or use it in combination with other glaucoma medications.

Like Vyzulta, Rhopressa has once-per-day dosing, which is beneficial in noncompliance, a well-known problem in glaucoma treatment. Mechanistically, Rhopressa works in a novel way, primarily on the trabecular meshwork as a rho-kinase (ROCK) inhibitor. This novel molecule targets the actin and myosin in the trabecular meshwork. No systemic contraindications are known with Rhopressa. Ocular adverse events include conjunctival hyperemia (54.4%), corneal verticillate (20.9%) and conjunctival hemorrhage (17.2%).[15]

In clinical trials with Rhopressa, cornea verticillata was localized to the basal corneal epithelium, subjects were asymptomatic, and the onset ranged from six to 13 weeks.[15] No reported cases of vision loss or reduced acuity with the cornea verticillata were reported.

Mechanistically, cornea verticillata occurs due to phospholipidosis and phospholipid accumulation, as in the case of amiodarone corneal whorls. Conjunctival hemorrhages were small petechial hemorrhages, and researchers now believe it to be more of a vasodilatory process.[15] Rhopressa provides 4mm Hg to 5mm Hg IOP reduction in patients with high and low IOPs, which is great news, as it is inherently difficult to decrease low IOP. Clinical trials indicate that Rhopressa does a consistent job in lowering a low IOP, and, over a 12-month period, researchers noted no tachyphylaxis.[15]

Consider using as monotherapy in patients who:

- Have concerns about the ocular side effects of prostaglandins.
- Are intolerant to or have inadequate efficacy with prostaglandins.
- Need or prefer alternative to beta blockers, alpha agonists, carbonic anhydrase inhibitors (CAIs).

Consider using in combination with:

- A prostaglandin analog.
- Other adjunctive agents.
- Glaucoma surgery, when desired IOP is not achieved.

Xelpros, approved in September 2018, is indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Xelpros is the first latanoprost product not formulated with the preservative benzalkonium chloride and uses potassium sorbate 0.47% as the preservative instead.[17] Research shows it can reduce IOP in patients with open-angle glaucoma and ocular hypertension up to a mean of 6mm Hg to 8mm Hg in randomized clinical trials.[16] Benzalkonium chloride can be a great preservative for multidose bottles but may also contribute to ocular surface disease.

The hope is that this formulation will help support the ocular surface, as long-term medical therapy with drugs poses this challenge for the patient and practitioner.[17] Xelpros is not available at pharmacies, as it is only available by the "direct pay" method as discussed previously.

Clinical Trials

Roclatan (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% by Aerie pharmaceuticals may be our next non-beta blocker fixed combination

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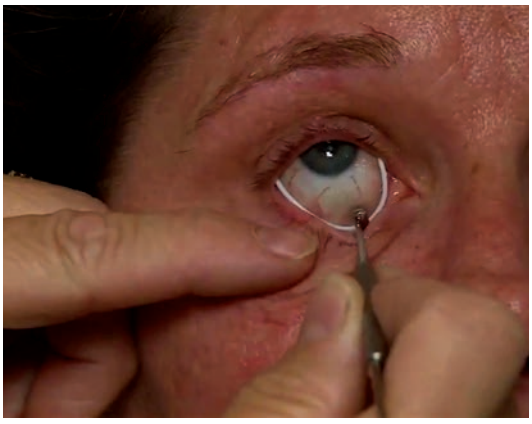

A single administration of the bimatroprost-laden ring implant provided sustained reduction of IOP in its Phase III trial.

drop as the Prescription Drug User Fee ACT (PDUFA) date is set for this month. This once-daily drop will be the first prostaglandin combination drop approved in the United States. This formulation has a great potential by coupling the powerful IOP lowering of latanoprost with the additional lowering of a low IOP ability of netarsudil.[18]

Implants and Injectables

Noncompliance is well-known as a problem in topical glaucoma care and is a key factor for the progression of glaucoma.[1,2] Research and development are occurring at all levels of glaucoma treatment to reduce the burden of eye drops. Sustained release modalities are in clinical trials to help address this well-known problem.

Phase III. Allergan is taking on the challenge by working on the Bimatoprost SR (sustained release) implant. This biodegradable implant is undergoing a Phase III clinical trial with its indication for IOP lowering for patients with primary open-angle glaucoma (POAG) or ocular hypertension. This implant is injected into the anterior chamber. Results recently released by Allergan show a 30% reduced IOP over a 12-week primary efficacy period and met predefined criteria for noninferiority to the comparator timolol.[19] This implant is designed to lower IOP for four months and seems to be well-tolerated thus far.[19] Allergan plans to file a new drug application most likely in the second half of 2019.

In an external approach to sustained release, Allergan acquired from ForSight Labs a compliant bimatoprost-laden ring (formerly called Helios), which sits in the ocular fornices. Based upon its comparatively large size, high quantities of medication and multiple drugs can be placed in a single device. Retention and comfort seem to be fairly good with this product, with an approximated 20% IOP reduction.[20]

Phase II. Glaukos, known for the iStent and iStent inject MIGS procedures, is currently investigating a travoprost-eluting intratrabecular implant. Slated for 2021-2022, iDose Travoprost is a titanium implant (1.8mm x 0.5mm) designed for continuous drug delivery directly into anterior chamber. The implant is filled with a novel and reportedly potent formulation of travoprost delivered via membrane-controlled Fickian elution once it is implanted. This injectable procedure is anchored in place and facilitates straightforward exchange upon drug depletion.

Another external platform for sustained release involves an intracanalicular punctum plug-based sustained-release drug system for the prostaglandin analog, travoprost (OTX-TP; Ocular Therapeutics). In clinical studies, the sustained-release OTX-TP was able to reduce IOP by 24% at day 10 (with nearly 90% of plugs still in place) and 15.6% at day 30 (but with only 42% of plugs still retained).[20]

Continuous-release device. Amorphex has developed the Topical Ophthalmic Drug Delivery Device (TODDD), a soft structure that can deliver drug to the eye continuously, around the clock for multiple months without interruption. The patient wears the TODDD under their eyelid and is replaced at prescribed intervals of weeks to months, depending on the condition being treated.[22] This non-invasive technology is attempting to solve the challenges of repetitious daily eye drop dosing, as well as difficulties with drop instillation, partial dosing, daily forgetfulness and continuing adherence to therapy.[21] Amorphex has timolol and timolol/prostaglandin in the pipeline.[22]

Looking Forward

The question remains as to whether patients will accept sustained drug delivery devices despite the apparent improvement in adherence to therapy. One recent report administered electronic surveys to 150 patients at two glaucoma clinics.[23] Participants were questioned on their willingness to accept: drug-eluting contact lenses, ring inserts, punctal plugs and subconjunctival injections as alternatives to IOP-lowering eye drops based on various success levels. Most glaucoma patients considered sustained drug-delivery modalities acceptable alternatives to IOP-lowering eye drops, but only could obviate surgery or demonstrate greater efficacy than eye drops.[24]

Overall, the past two years have brought about great change in the

world of glaucoma treatment. Not only do we have novel mechanisms of action in the drug side of treatment, but we have the benefit of gaining experience, as laser therapies and minimally-invasive procedures become more prevalent. Additionally, sustained release inserts offer a new and exciting opportunity to improve compliance in patients with glaucoma. ■

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Dr. Offerdahl is an assistant professor of biomedicine at Salus University.

Dr. Sowka is chief of advanced care and director of the glaucoma service at Nova Southeastern University College of Optometry.

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PEER-REVIEWED PRA ARTICLE

Anti-VEGF: Where Are We Now?

This review looks into the years of research on this versatile class of medications and turns an eye to its future. **By Bill Kress, OD**

The mid-2000s were an exciting time in retina care. First, the FDA approved Macugen (pegaptanib, then from Eyetech, now Bausch + Lomb) for wet age-related macular degeneration (AMD) in December 2004. It showed some ability to maintain, but not improve, vision. That alone was a boon in an era when steady, progressive decline was the fate of most AMD patients. A year later, Avastin (bevacizumab, Genentech) was shown to be effective in restoring lost vision, introducing a low-cost but off-label treatment—and beating to market the same company's branded drug Lucentis (ranibizumab, Genetech), which arrived in 2006. A third option, Eylea (aflibercept, Regeneron), was approved in 2011.

These ground-breaking therapies revolutionized retinal vascular disease management and set a new standard of care. Today, they are first-line treatments for most cases of neovascular AMD.[1] All work by targeting vascular endothelial growth factor (VEGF).

Beginning in the 1970s, with confirmation in 1989, research identified VEGF as a growth factor necessary for tumor angiogenesis.[2-4] VEGF also promotes vascular permeability. A 1994 study showed retinal hypoxia inducing intraocular VEGF release correlating with neovascularization in primates.[5] Several human and primate studies to follow demonstrated VEGF played a direct role in the stimulation of intraocular neovascularization, and significant VEGF was found within intraocular fluid of patients with active neovascularization.[6-11]

This article will review both the

Table 1. Currently Employed Anti-VEGF Treatment Options

DRUG NAME	FDA INDICATION	ASSOCIATED CLINICAL TRIALS
Eylea	• Wet age-related macular degeneration • Diabetic retinopathy (all forms) • Diabetic retinopathy in diabetic macular edema • Macular edema from retinal vein occlusion	• VIEW 1 and 2 • PANORAMA/DRCR.net Protocol W • VIVID/VISTA • COPERNICUS/GALILEO/ VIBRANT • VIEW1/2
Lucentis	• Wet age-related macular degeneration • Diabetic retinopathy (all forms) • Diabetic retinopathy in diabetic macular edema • Macular edema from retinal vein occlusion • Choroidal neovascularization in myopic degeneration	• ANCHOR/MARINA • DRCR.net Protocol S • RIDE/RISE • BRAVO/CRUISE • HORIZON/CATT • VIEW
Avastin	Off-label	CATT

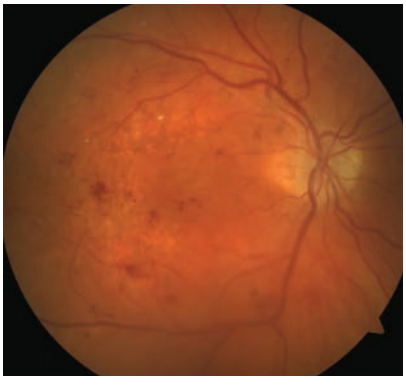

Fig. 1. This fundus photo of a 71-year-old patient's right eye shows moderate nonproliferative diabetic retinopathy with diabetic macular edema.

academic literature and industry-sponsored investigations into this sight-preserving class of medication. It will also review two clinical examples of patients receiving injections as well as examine where anti-VEGF therapy stands today.

Ongoing Trials

Anti-VEGF therapy has become the standard of care for a host of intraocular vascular diseases. Eylea, Lucentis and the off-label use of Avastin are providing patients effective treatment and the ability to receive alternative treatment options during management (*Table 1*). As demonstrated in the CATT and IVAN trials comparing Avastin and Lucentis for wet AMD—as well as the VIEW 1 and VIEW 2 trials comparing varying dosages of Eylea and Lucentis for wet AMD—retina specialists can decide the best course of treatment based upon availability and other external factors, such as cost to the patient, without compromising quality of care.[12-15]

With the available anti-VEGF agents, current research is continuing to improve upon optimal treatment delivery.[11-14] As of August 2018, the FDA approved a supplemental Biologics License Application for the use of Eylea every 12 weeks following one year of successful therapy on an every-four-week or every-eight-week regimen based on the Phase III outcomes of VIEW 1 and VIEW 2 clinical trials.[16] This means some patients can receive injections quarterly as opposed to every eight weeks. Decreasing injection frequency may also impact long-term outcomes of wet AMD, as previous studies found more frequent doses may increase the potential for geographic atrophy (GA).[12,13,17]

A few of the ongoing clinical trials are:

• **CAN-TREAT,** assessing Lucentis dosage and extended frequency for wet AMD.

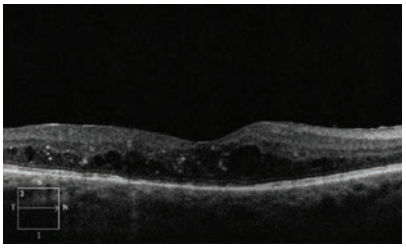

Fig. 2. This OCT of the same eye from Figure 1 shows intraretinal fluid consistent with diabetic macular edema.

• **LUMINOUS,** assessing five-year outcomes of safety, efficacy, treatment patterns and quality of life for wet AMD using Lucentis.

• **RIVAL,** comparing Lucentis and Eylea using a treat-and-extend regimen and subsequent development of GA over a two year period, as presented as interim data at the 17th EURetina Congress in Barcelona.[18-20]

These ongoing studies will provide results in the next one to four years and aim to give clinicians the best practice guide in managing wet AMD patients with current anti-VEGF options.

The benefits of anti-VEGF treatment for visually significant DME and proliferative diabetic retinopathy (PDR) is clearly defined (*Table 1*). Recently published data from the PROTEUS study shows that Lucentis plus panretinal photocoagulation (PRP) is more beneficial for regression of neovascularization in high-risk PDR than PRP alone.[20] The CLARITY non-inferiority trial found that Eylea is superior in preserving acuity at one-year than standard-of-care PRP.[21] Current research involving the treatment of nonproliferative diabetic retinopathy (NPDR) and asymptomatic DME with anti-VEGF therapies is looking to provide more concise clinical guidelines for patients who may commonly be under observation only. In addition to already-approved Lucentis for DR (with AMD without macular edema), Regeneron will look to obtain FDA approval for Eylea's use in moderate to severe NPDR without macular edema. Based on preliminary results of the PANORAMA study, as well as preliminary results from DRCR.net Protocol W, Regeneron will look to expand its market options for Eylea.[22,23]

DRCR.net Protocol V is an ongoing trial assessing the management of DME with very good vision (20/25 or better) with observation plus deferred anti-VEGF prompt focal laser plus deferred anti-VEGF, or prompt Eylea.[24]

The Pipeline

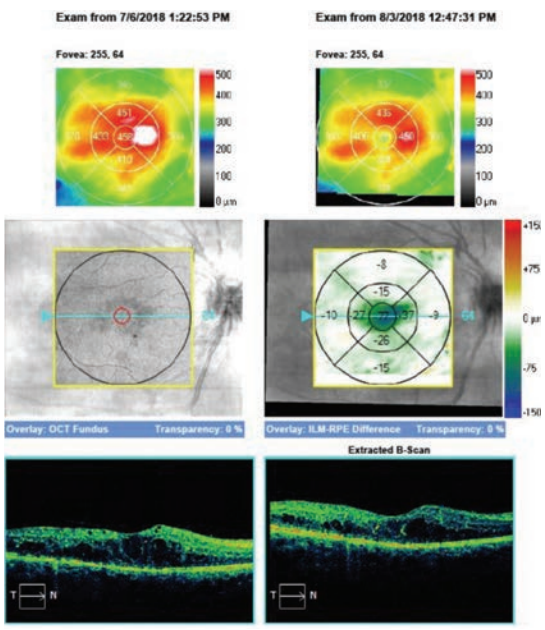

Fig. 3. Progression analysis on OCT of the right eye of the patient in Case One, four weeks after initial intravitreal injection of anti-VEGF medication.

The future of anti-VEGF treatment for retinal vascular conditions appears promising. In addition to ongoing studies involving optimization of current FDA-approved therapies, several new options are promising as either stand-alone options or adjunctive therapies to existing anti-VEGFs.

• **Brolucizumab (Novartis).** This humanized, single-chain antibody fragment inhibitor of VEGF with a molecular weight approximately four and a half times smaller than Eylea and two times smaller than Lucentis allows for greater molar concentration per injection and possibly will offer greater retinal tissue penetration and extended duration of treatment per injection.

Phase III HAWK and HARRIER trials compared Eylea 2mg every eight weeks with brolucizumab 3mg and 6mg every 12 weeks following three monthly loading doses for wet AMD.[25,26] The study demonstrated non-inferiority between the two medications. Brolucizumab showed significantly reduced disease activity at week 16, superior central thickness improvements at week 16 and week 48, significantly fewer patients with intraretinal or subretinal fluid and overall safety compared with Eylea 2mg. Data reported at the American Academy of Ophthalmology 2018 meeting reaffirmed that, at 96 weeks, patients had improved retinal fluid, central retinal thickness and visual gain with brolucizumab 6mg vs. Eylea 2mg.

• **Abicipar (Allergan).** This anti-VEGF-A designed ankyrin repeat protein (DARPin) is highly specific, has high-affinity target binding proteins is being developed by Molecular Partners and Allergan. DARPins are recombinant proteins genetically engineered to bind to a specific protein, making them more potent, amenable to a better shelf life and highly soluble, which means they can be easily mixed with other agents for treatment. Data from the Phase II PALM study indicate abicipar injected every eight or 12 weeks in patients with DME fared as well as Lucentis 2mg injected every month.[27] Initial Phase III results of the SEQUOIA and CEDAR clinical trials comparing every four-week dosing of Lucentis to every 12-week and every eight-week dosing of abicipar for wet AMD demonstrated noninferiority between the two medications with a primary endpoint of proportion of treated patients with a stable acuity at 52 weeks.[27-29] These trials have a protocol assessing the primary endpoint out to 96 weeks and are ongoing at the time of publication.

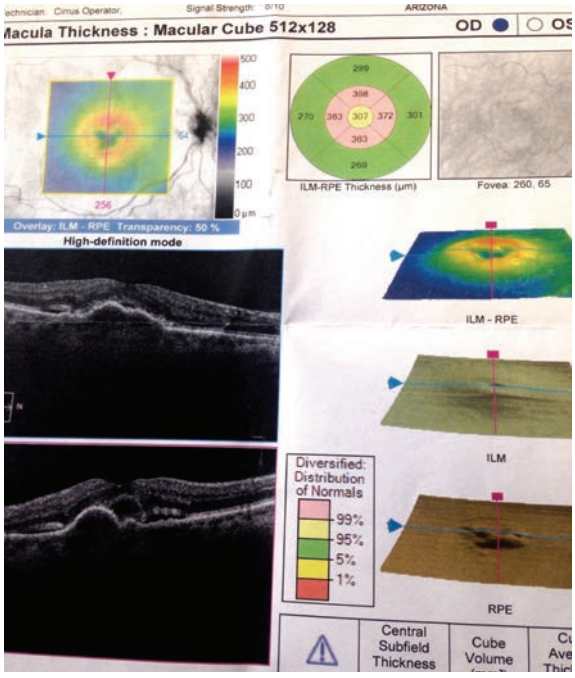

Fig. 4. This OCT of the case two patient's right eye at her first visit shows PED and associated subretinal and intraretinal fluid.

• **OPT-302 (Opthea).** This VEGFR-3 molecule blocks the activity of VEGF-C and VEGF-D. Currently in Phase II clinical trials, researchers are exploring OPT-302 0.5mg and 2.0mg as a combination therapy with Lucentis 0.5mg in wet AMD patients. Early results appear promising for OPT-302 as an adjunctive therapy in patients responding poorly to VEGF-A therapy alone.[30]

• **Conbercept (Chengdu Kanghong Biotech).** This recombinant fusion protein that binds all VEGF-receptor isoforms and PIGF is currently marketed in China for wet AMD. Conbercept received Phase III clinical trial fast-track in the United States under the PANDA 1 trial comparing conbercept 0.5mg (every eight weeks) and 1.0mg (every 12 weeks) vs. Eylea 2.0mg (every eight weeks) after three total monthly loading doses.[31] Although clinical trials are ongoing for conbercept, research shows it is promising, with greater VEGF and PIGF binding affinity than Lucentis 0.5mg.[32,33] Conbercept, under the BRAVE trial, is also being assessed in Phase III clinical trials for macular edema associated with branch retinal vein occlusion.[34] Data collection is ongoing for this study and is comparing conbercept to sham injections.

• **Ziv-aflibercept (Sanofi-Aventis/Regeneron).** A recombinant fusion protein with similar actions on VEGF isoforms and PIGF as Eylea, ziv-aflibercept is currently FDA-

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[1] Schanzlin, Olkowski, Coble, Gross. NuLids II Study, April 2018

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Two Anti-VEGF Uses in Clinical Practice

Case One

Visit 1: A 71-year-old Caucasian male presented to our clinic for an unscheduled follow-up examination. He reported blurred vision in his right eye for the past two months at distance and near with and without glasses. Past ocular history was positive for visually insignificant cataracts bilaterally and a posterior vitreous detachment (PVD) in the right eye that was longstanding. He also had a history of mild non-proliferative diabetic retinopathy with previous focal laser for diabetic macular edema in both eyes at his exam more than a year ago. His past medical history was positive for gout, hyperlipidemia, benign prostatic hypertrophy, Type 2 non-insulin-dependent diabetes mellitus and obstructive sleep apnea, for which he was taking allopurinol, pravastatin, tamsulosin and metformin. He was also taking over-the-counter fish oil supplements daily, as well as glucosamine daily. The patient had no known allergies.

Entrance testing yielded best-corrected distance acuities of 20/70- OD and 20/30 OS. His pupils were round and reactive to light without afferent pupillary defect in either eye. Confrontation visual fields were full to finger counting in each eye. Subjective refraction yielded no visual acuity improvement at distance with any lens in the right eye. Intraocular pressure using Goldmann tonometry yielded 13mm Hg OD and 14mm Hg OS at 09:38am. A slit lamp exam revealed mild dermatochalasis, conjunctivochalasis, and 1+ nuclear sclerosis in both eyes.

Dilated fundus exam revealed 0.10 cup-to-disc ratios and good color in each eye. The retinal vascular assessment yielded mild attenuation in each eye with mild arterio-venous crossing changes. Posterior pole evaluation showed intraretinal hemorrhages throughout arcades and into macula in both eyes with a few exudates in superior macula of the right eye only (*Figure 1*). The peripheral retina was flat and intact in both eyes. Optical coherence tomography (OCT) was performed on the macula (*Figure 2*). The patient was diagnosed with moderate nonproliferative diabetic retinopathy with diabetic macular edema and referred to our retina clinic for evaluation and treatment.

Visit 2: He was examined by our retinal specialist two weeks later. His best corrected visual acuity remained unchanged from the initial exam. The patient received a single injection of Eylea 2.0mg in the right eye.

Visit 3: The patient was re-examined by the retinal specialist four weeks later. His best-corrected visual acuities at that exam measured 20/40 OD and 20/30 OS. A macular OCT was performed and demonstrated significant improvement in the central retinal thickness (*Figure 3*). At date of publication, the patient will be awaiting follow-up care.

Case Two

On May 16, 2018, a 65-year-old female—my own mother-in-law, in fact—called complaining of sudden vision changes in her right eye. She was advised to seek immediate eye care with her local providers.

Visit 1: Two days later, she presented to the retina center with a complaint of sudden, mild blurring of her right eye. Her past ocular history was positive for visually insignificant nuclear sclerosis OU. She has a positive family history of AMD (mother). Past medical history was positive for hypothyroidism, for which she is taking levothyroxine daily. The patient had no known allergies.

Entrance testing yielded a corrected distance acuity of 20/30- OD with a prescription of -0.50 DS and 20/20 OS with a prescription of -0.50 DS. Pupils were round and reactive to light without afferent pupillary defects in either eye. Confrontation fields were full to finger counting in each eye. Subjective refraction yielded no visual acuity improvement at distance with any lens in the right eye. Intraocular pressure using Goldmann tonometry yielded 15mm Hg OD and 15mm Hg OS at 9:25am. Slit lamp exam was relatively unremarkable with grade 1+ nuclear sclerosis in both eyes.

Dilated fundus exam revealed 0.10 cup-to-disc ratios and good color in each eye. Retinal vascular assessment was unremarkable. Posterior pole evaluation showed a pigment epithelial detachment (PED) of the right macula with subretinal fluid, and mild drusen in both maculae. The peripheral retina was flat and intact in both eyes. OCT was performed on the macula (*Figure 4*).

The patient was diagnosed with exudative AMD in the right eye with active choroidal neovascularization and moderate dry AMD in the left. Fluorescein angiography was not performed to confirm this diagnosis. The retina specialist elected to begin treatment at that exam with intravitreal Avastin (IVA). The patient was to follow up in four weeks with a different retinal group upon returning home. She was also instructed to begin one AREDS2 tablet, twice a day.

Summary of Visits 2-6: Upon her return home, the patient was examined four weeks after her initial IVA administration (*Table 2*). OCT change analysis between Visit 3 and Visit 5 (*Figure 5*) and OCT for Visit 6 (*Figure 6*) are provided. Despite diligent follow up care, the response to IVA and intravitreal Lucentis (IVL) was not ideal. At time of publication, the patient will return to clinic to receive intravitreal Eylea (IVE).

Table 2. Summary of Case Two

EXAM DATE	BEST-CORRECTED ACUITY OD	TREATMENT
06/18/18	20/30-2	IVA
07/26/18	20/30-2	IVA
08/23/18	20/50+2	IVA
10/01/18	20/60	IVL
11/02/18	20/70	IVL

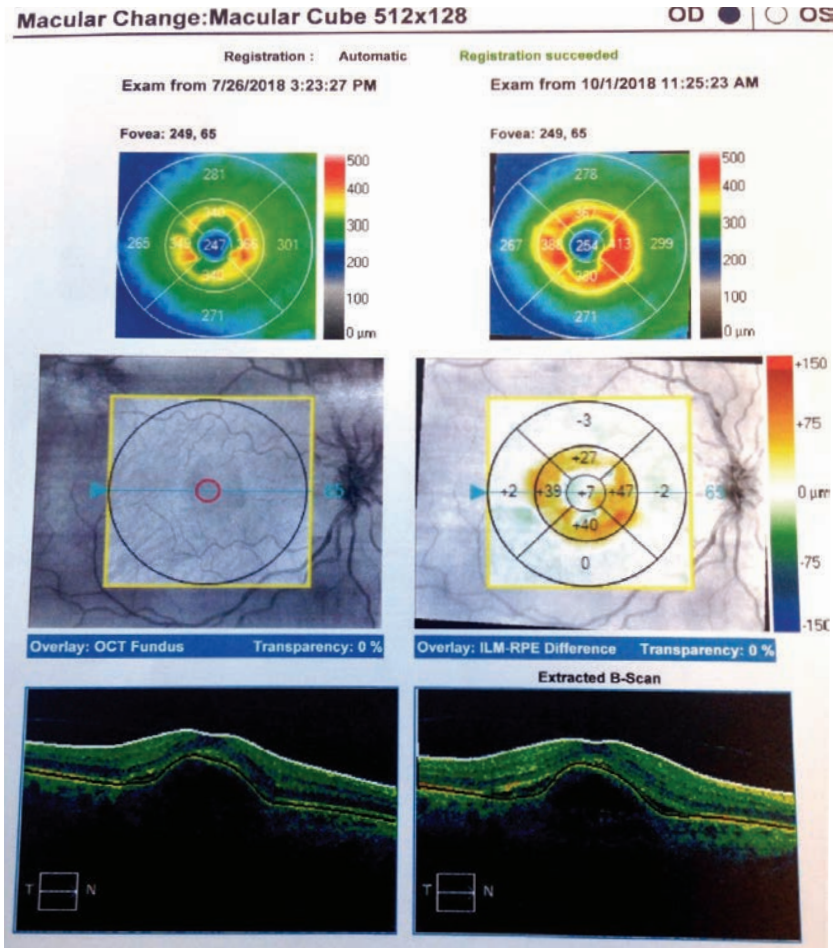

Fig. 5. Here, our Case Two patient's change analysis between visits three and five are displayed. You can see PED and associated intraretinal and subretinal fluid. Note the worsening of overall thickness.

approved for metastatic colorectal cancer treatment. Previous studies looked at its potential toxicity to the retinal tissue, given its osmolarity, but these reports found no significant complications relative to certain levels of concentration.[35,36] Current FDA clinical trials, such as ZALTRAP, aim to provide greater insight into toxicity and overall efficacy in several retinal conditions, including wet AMD, DME and macular edema due to retinal vein occlusion. Estimated study completion for ZALTRAP is December 2019.[37] Another ongoing FDA trial, ZEBRA, will compare ziv-aflibercept 1.25mg every month vs. Eylea, Lucentis and Avastin every five to 12 weeks in patients with wet AMD to assess the overall best-corrected visual acuity outcomes.[38] Data from ZEBRA may not be available until 2020 based on estimated study completion date.

• **Faricimab (Genetech).** This is the first bispecific antibody designed specifically for intravitreal use to simultaneously bind angiopoietin-2 (Ang-2) and VEGF-A with high potency and specificity. The Phase II STAIRWAY study demonstrates that faricimab 6.0mg every 16 weeks or every 12 weeks is comparable with ranibizumab 0.5mg every four

weeks in overall improvement of acuity and central retinal thickness after a 52-week follow-up.[39] The safety profiles of the two drugs are comparable, too.[39]

Two Phase III studies—RHINE and YOSEMITE—are designed to investigate the efficacy and safety of faricimab compared with aflibercept in patients with DME.[40,41] Additionally, in response to the STAIRWAY study, a global Phase III study for faricimab in wet AMD will commence in 2019.

• **Port delivery system (PDS) with ranibizumab (Genentech).** This refillable, sustained-delivery system is implanted into the globe to deliver varying dosages of Lucentis. In the Phase II LADDER study, doses of 10mg/mL, 40mg/mL, 100mg/mL ranibizumab were placed in the port-delivery system for patients with wet AMD.[42] Outcomes show the medication refill was not needed for up to six months or longer and best-corrected visual acuity for the 100mg/mL dose was comparable with monthly Lucentis 0.5mg injections. The Phase III ARCHWAY trial will assess long-term acuity in patients with the PDS refilled every 24 weeks vs. monthly Lucentis 0.5mg.[43]

• **Biosimiliars.** These biological products are highly similar to, and have no clinically meaningful differences from, existing FDA-approved reference products. Unlike generics, whose active ingredients are the exact same as the approved referenced drug, biosimiliars must demonstrate that they are highly similar to the reference product, except for minor differences in clinically inactive components, and that they demonstrate no clinically meaningful difference in safety or efficacy.[43] Currently biosimiliar products used outside of the United States are under Phase III investigation and demonstrate noninferiority to Lucentis.[44]

• **RGX-314 (RegenXBio).** This formulation is being developed and studied as a one-time subretinal gene therapy treatment for wet AMD. It includes a recombinant adeno-associated virus gene therapy vector that carries a coding sequence for a soluble anti-VEGF protein. RGX-314 The expressed protein is designed to neutralize VEGF activity, modifying the pathway for formation of new leaky blood vessels and retinal fluid accumulation. Patients are currently being enrolled in Phase I/IIa, open-label, multiple-cohort, dose-escalation study designed to evaluate the safety and tolerability of RGX-314 gene therapy in subjects with previously treated wet AMD.[45]

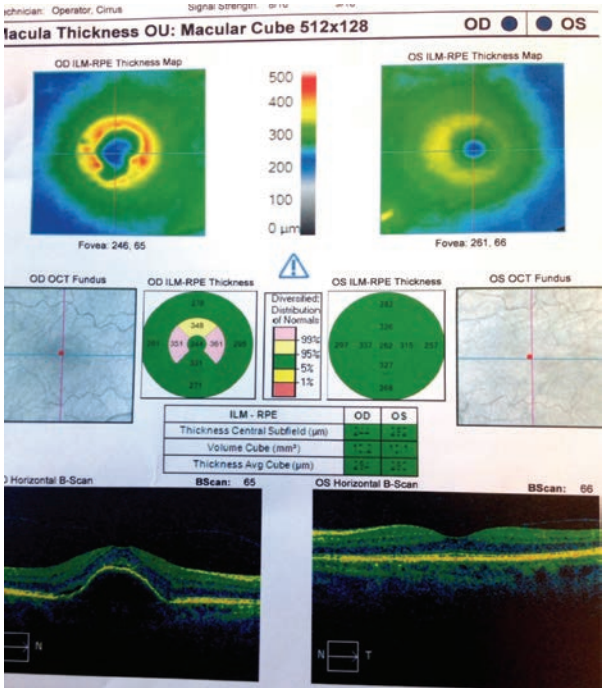

Fig. 6. These OCT images show our Case Two patient at her sixth visit. You can see persistent PED with minimal intraretinal fluid in the right eye. Additionally, her left eye shows minimal RPE changes from drusen and no fluid.

Anti-VEGF therapy has developed into the new standard of care for patients with retinal vascular disease. The advent of these medications has brought about the ability to restore and maintain vision. The future of retinal vascular care with anti-VEGF agents now depends on the ability to use existing products more effectively and efficiently, or to build upon their successes by creating next-generation drugs that address shortcomings of the initial wave. Additionally, the market is looking to provide clinicians with new options to manage these myriad conditions with optimal intraocular drug delivery and efficacy without compromising the patient's vision, ocular health, time or finances. ■

Dr. Kress is an optometrist at the Cincinnati Veteran's Administration Medical Center.

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PEER-REVIEWED PRA ARTICLE

Red Eye Roundup

This symptom could be a harbinger of many conditions. Here's a look at the common causes and what to do about them. By An Vo, OD, and Jim Williamson, OD

The red eye continues to be a common problem in both ophthalmic and primary medical care practices. Although little epidemiological data exists on the red eye presentation, it doesn't take a comprehensive study to recognize the socioeconomic impact it has on our population. Lost school and work time and the cost of medical visits and prescriptions often exacerbate patient suffering. When the condition presents, optometrists can minimize these red eye burdens with an accurate diagnosis and prompt initiation of treatment, even if it is palliative.

Getting Started

As with any office visit, a thorough history is crucial (*Table 1*). After the history, clinicians should start the localization process with a gross examination outside of the slit lamp with the room lights on. Specifically, take note of the patient's skin, face, hands and nails. Sometimes the answer can be right in front of us, as in cases of rosacea-related rhinophyma. Most importantly, have the patient look in all positions of gaze. This provides a de-magnified view, which can help you detect intra- or inter-eye asymmetries, in addition to an adequate adnexal observation.

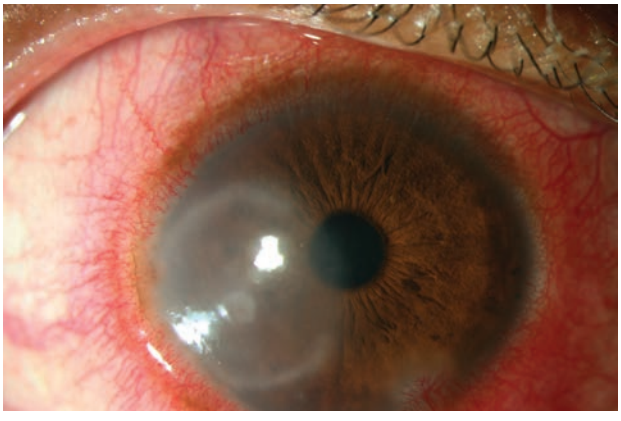

Fig. 1. Intense ciliary flush from pepper spray exposure.

The eye appears red due to blood vessel dilation. Ciliary injection, which results from dilation of anterior ciliary artery branches, implies inflammation of the cornea, iris or ciliary body (*Figure 1*).[1] Conjunctival injection, however, is due to dilation of the more posterior and superficial conjunctival vessels, which causes a more dramatic injection.[1] Though not often used, conjunctival grading scales exist to help get an accurate and consistent assessment of bulbar redness both between visits and among group practitioners.[2] External photography is another option.

As always, start the visual exam with an acuity assessment. If needed, use a topical anesthetic with a patient with corneal abrasion or foreign body. The only acceptable deferral would be with acid or alkali injuries, which are a true ocular emergency and prompt irrigation

takes precedence over acuity measurement. Pupil and extraocular motility evaluation is key to check for a mid-dilated pupil seen in angle closure or muscle restriction consistent with orbital cellulitis.

During slit-lamp biomicroscopy, gauge the severity of any photophobia. Evert both upper and lower lids and pay particular attention to the lower lid, as sometimes a conjunctival foreign body hides within a fold in the palpebral fissure. For conjunctivitis, identify the type of morphological response: papillary, follicular, membranous/pseudomembranous, cicatrizing or granulomatous.

Next, instill staining agents such as fluorescein, and remember that rose bengal stings more than lissamine green. Always evaluate the other eye in cases of unilateral disease but be careful about cross-contamination in suspected viral cases.

When measuring intraocular pressure (IOP), disinfect the applanation tonometer properly with 1:10 diluted bleach, as recommended by both tonometer manufacturers and the Centers for Disease Control and Prevention.[3] Alcohol wipes with 70% isopropyl alcohol and 3% hydrogen peroxide are not advised. Alternatives to determine IOP include disposable tonometer tips, rebound tonometry and devices with protective covers.

Following a thorough anterior segment evaluation, the decision to dilate varies between practitioners and depends on the exam findings or history. For instance, reduced vision would certainly be a reason to fully evaluate the fundus. Another example would be the report of a high-speed foreign body, which could potentially penetrate the eye.

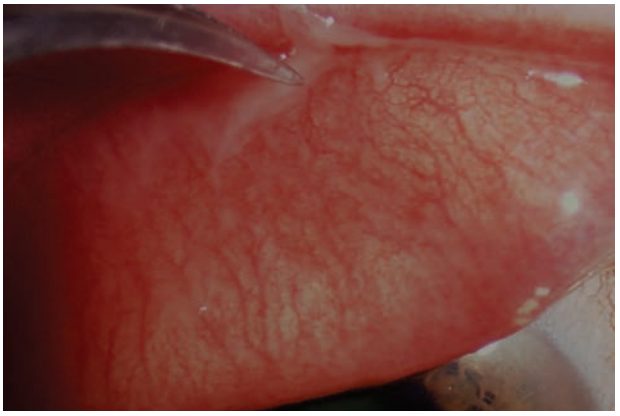

Fig. 2. Forceps removal of a pseudomembrane in viral conjunctivitis.

Clinical acumen determines the next course of action. Following red eye algorithms—plenty of which exist—may be beneficial. While not an all-inclusive list, some common diagnoses include (*Table 2*):

Viral Conjunctivitis

Conjunctivitis is the most common cause of red eye, and viral is the most encountered variant. Follicles are the classic clinical sign, though they can also be seen in chlamydia and medicamentosa. The adenovirus serotypes are responsible for acute nonspecific follicular conjunctivitis, chronic keratoconjunctivitis, pharyngoconjunctival fever (PCF) and epidemic keratoconjunctivitis (EKC). All forms exhibit preauricular lymphadenopathy, so palpate lymph nodes for all suspected cases.

Nonspecific follicular conjunctivitis displays mild signs and symptoms, including conjunctival hyperemia and lid edema. The disease course, which lasts about three weeks, can range from self-limiting to severely visually debilitating. Adequate caution should be stressed to prevent spreading the virus to the patient's immediate family and coworkers. Chronic conjunctivitis lasts longer, may recur after months of dormancy and usually coincides with an upper respiratory infection. PCF presents with pharyngitis and fever, is highly infectious and is often transmitted through personal contact, swimming pools or fomites.

PCF treatment is mostly palliative, unless pseudomembranes are present (*Figure 2*). Patient education is crucial and should include avoiding shared contact, disinfecting and cleaning any potential viral reservoirs and frequent hand washing. Children and adults should avoid any school or work duties for as long as permissible until the condition resolves due to the propensity of the adenovirus to spread.

Povidone-iodine—traditionally used for disinfection prior to surgery—shows strong promise as a method of controlling adenovirus populations in EKC. One study found povidone-iodine dramatically reduced adenoviral titers compared with 0.1% dexamethasone and artificial tears.[4] The treatment also improved discharge, hyperemia, superficial punctate keratitis and pseudomembrane formation. Although povidone-iodine comes in a 5% sterile solution, the researchers found no benefit for concentrations higher than 1% against adenovirus.[4]

Allergic Conjunctivitis

A dramatic increase in allergic disease has occurred in the last few decades, making allergic conjunctivitis a frequently encountered condition.[5] This bilateral pathology, which can be seasonal (90% of cases) or perennial, exhibits eyelid edema, conjunctival injection and serous to mild mucous discharge.[6] Periorbital venous congestion, known as "allergic shiners," appears

as dark circles in the lower adnexa and results from a pooling of blood secondary to swelling in the sinus cavities. Itching represents the hallmark symptom. Typical associated factors include environmental allergens such as grasses and pollens, outdoor pollution, smoke exposure and contact with animals such as dogs and cats. A history of atopy in the presence of corneal signs of disease and decreased corrected spectacle acuity may warrant a corneal topography to assess for atopic-related keratoconus.

As an initial treatment for allergic conjunctivitis, practitioners may counsel patients to take simple steps such as reducing exposure to an allergen and using cold compresses, artificial tears and eyelid hygiene. Research shows a therapeutic effect on the signs and symptoms of allergic conjunctivitis using cold compresses and artificial tears alone after controlling for pollen exposure.[6] Topical ocular agents—alone or in conjunction—are another option. The decision for prescription or over-the-counter medications varies with practitioner and disease severity. An allergy consult may be indicated for patients who fail to respond to treatment.

Table 1. Taking a Red Eye History

Symptoms	Itching, burning, tearing, discharge (purulent, mucous, serous), pain, foreign body sensation, photophobia, diplopia, blurred vision
Onset and Course	Duration, acute vs. chronic, progressive or stationary
Location	Unilateral or bilateral
Ocular History	Previous episodes, prior exposure to infected people, trauma or chemical injury, contact lens wear, use of topical or over-the-counter drops; current attempted therapies
Medical History	Recent upper respiratory infections or illness, atopy, dermatology conditions, thorough review of systems, current medications
Social History	Environmental factors (computer use, occupation, hobbies, smoke exposure, sexual history, if applicable)

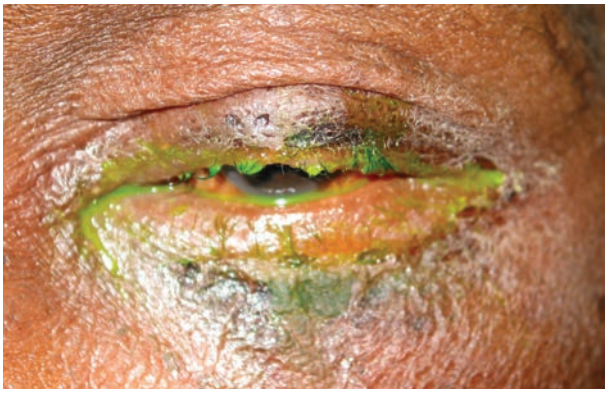

Fig. 3. Madarosis and purulent discharge in a patient with a bacterial infection.

Bacterial Conjunctivitis

This is the second most common cause of infectious conjunctivitis, with one study estimating an incidence of 135 in 10,000 individuals annually in the United States.[7] The true incidence of bacterial conjunctivitis, however, is more difficult to determine, as practitioners treat most cases empirically without culture, and many cases are self-limited and resolve without intervention.

The most common etiologies include *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenza*.[8] Straightforward cases can be treated with a broad-spectrum fluoroquinolone. For pediatric cases, Polytrim (Allergan) is an excellent first option because of its additional coverage of *H. influenza*.

Patients typically present with purulent discharge and bilateral involvement. Further classification is based on severity and presence of membranes, papillae or follicles, as well as culture, if appropriate. Knowing the duration of illness and onset (i.e., acute, hyperacute or chronic) is key when obtaining a history and can quickly narrow the list of differentials.

Chronic bacterial conjunctivitis often involves matted, crusted lashes, which provide a large surface area for bacteria to reside (*Figure 3*). This leads to trichiasis, telangiectasia, hordeola and madarosis. Predictably, this sizable bacterial load can cause inferior corneal staining and accumulation of discharge. *S. aureus* is the most common cause of chronic cases, followed by *Moraxella lacunata*, a rod-shaped gram-negative bacterium. In addition to the lids and lashes, the canaliculi and lacrimal sac can act as a reservoir of bacteria for *Actinomyces israelii* and S. *pneumoniae*, causing canaliculitis or dacryocystitis, which may present similarly to chronic conjunctivitis.

Acute bacterial conjunctivitis has a rapid onset with mucopurulent discharge, inflamed bulbar conjunctiva and papillae. Symptoms typically resolve within 14 days. Swollen lids, chemosis and excessive mucopurulent discharge indicate the rarer hyperacute form. Hyperacute cases may also present with pseudomembranes and tender preauricular nodes. Due to its strong association with *Neisseria gonorrhoeae* and *Neisseria meningitidis*, culture may be warranted in severe presentation. Explore the history for any sexually transmitted disease (STD) and consider blood work if the presentation rapidly progresses despite treatment.

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Chlamydia is the most common reportable STD in the United States and has an incidence of 2.9 million individuals.[9] Infection is caused by *C. trachomatis*, *C. pneumoniae* and *C. psittaci*. *C. trachomatis*, the causative organism for trachoma, produces a follicular response of both the upper palpebral and limbal bulbar conjunctiva. Eventual scarring of the latter area leads to Herbert's pits. Though rare in the United States, it poses a substantial risk in other countries with limited access to healthcare and hygiene.[10] However, adult inclusion conjunctivitis caused by *C. trachomatis* serotypes D-K is fairly common in the United States. This presentation is characterized by follicles of the palpebral conjunctiva—more so in the lower fornix—and discharge. Treatment options include 100mg of oral doxycycline twice daily or a single azithromycin dose of 1,000mg.[11]

A new broad spectrum antiseptic—povidone-iodine 0.6% with dexamethasone 0.1%—under investigation for both adenoviral and bacterial conjunctivitis is showing promise. In a Phase II trial, QID dosing showed a statistically significant improvement in rates of clinical cure and viral eradication compared with vehicle by day six.[12]

Dry Eye

Patients who complain of dry eye often also present with red eyes. But just because a patient complains of dryness doesn't automatically mean a diagnosis of dry eye. Practitioners must initiate a full dry eye workup that includes a validated dry eye questionnaire and tear break-up time, in addition to meibography (photography) or meiboscopy (transillumination) and expression to determine the meibomian gland status. An incomplete workup could lead to inappropriate and ineffective treatment (e.g., prescribing doxycycline in a patient with significant gland loss).

The debridement-scaling technique is useful to remove accumulated tissue and debris from the line of Marx (LOM) and keratinized lid margin.[13] To accomplish this, use a lateral motion with the golf club spud along the LOM to remove the lissamine green stained cells.

Clinicians must counsel patients about the chronic nature of dry eye disease. Exacerbations occur even with patients who are usually well controlled. Clinicians should recommend a specific artificial tear or lid scrub product to ensure the patient uses the best therapy for their specific dry eye condition (e.g., lipid-based, preservative-free). Other therapies include topical anti-inflammatories, fish oil, tetracyclines and moisture goggles, to name a few.

Episcleritis

This condition is usually diffuse or simple with benign, mild inflammation that resolves within days to weeks.[14] It is frequently located between the palpebral fissures.[15] Patients complain of mild discomfort or irritation and may present with epiphora. Because epislceritis involves the conjunctival and superficial episcleral plexi, the affected area appears bright red. This is in contrast to the deep episcleral plexus involvement with scleritis and the characteristic bluish-violet hue.[16] Additionally, IOP may be elevated due to increased episcleral venous pressure.[17]

Episcleritis is usually a self-limiting condition with nearly a 20% resolution rate without treatment, and patient education or topical lubricants may suffice.[14] Topical non-steroidal anti-inflammatory drugs provide no benefit over artificial tears.[18] Clinicians may elect to treat with a mild topical steroid.

A widely-used technique to differentiate episcleritis from scleritis is using phenylephrine to blanch congested conjunctival and superficial episcleral blood vessels. Some advocate using the 2.5% concentration, while others prefer 10%.[14,19] The deep episcleral plexus affected in scleritis should not blanch.

Table 2. Other Possible Red Eye Causes

- Vernal conjunctivitis
- Atopic conjunctivitis
- Toxic/chemical conjunctivitis
- Elevated episcleral venous pressure
- Angle closure
- Malignancies
- Peripheral ulcerative keratitis
- Mechanical (mucus fishing)
- Phlyctenular keratoconjunctivitis
- Giant papillary conjunctivitis
- Reactive arthritis
- Cicatricial pemphigoid
- Erythema multiforme
- Floppy eyelid syndrome
- Orbital pseudotumor
- Dacryocystitis
- Canaliculitis
- Trichiasis
- Entropion
- Hordeola
- Pinguecula
- Pterygia
- Corneal infiltrate/ulcer
- Limbal stem cell dysfunction (*Figure 5*)

Rosacea

Ocular rosacea occurs in 6% to 50% of patients with cutaneous rosacea.[20] Because cutaneous rosacea usually affects the face, simply looking at the patient can lead to its differential. Signs or symptoms include burning or stinging, telangiectaic lid margins, conjunctival injection, photophobia and blurred vision. It only takes one or more of these to diagnose ocular rosacea, according

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to the National Rosacea Expert Committee.[20]

About 20% of rosacea patients develop ocular manifestations first.[20] Contradicting early studies, reports of ocular rosacea in young children have dramatically increased over the past decade.[21] Making the diagnosis in this demographic has its challenges, given both the low suspicion for ocular rosacea and that facial manifestations usually present in patients older than 30 years of age.[21] If identified, tetracycline should be avoided.

Demodex infestation—both *D. folliculorum* and *D. brevis*—is more common in rosacea patients, though the mite's role in the condition remains unclear. This should be considered in cases refractory to typical ocular rosacea treatment.[22] Patients are often instructed to use lid scrubs for ocular rosacea, and some advocate 50% tea tree oil scrubs to address the *Demodex* concern.[23]

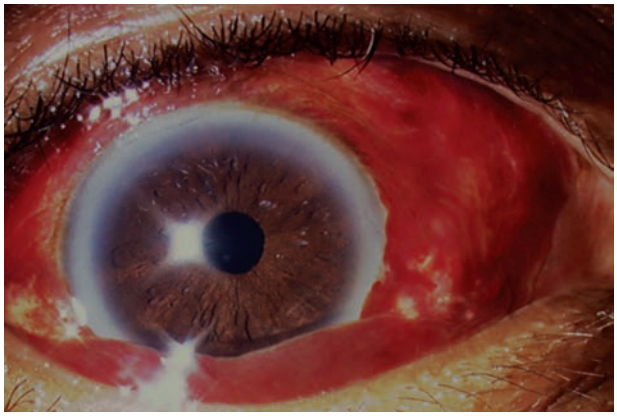

Fig. 4. Ocular lubricants were required in this case due to the bullous nature of the subconjunctival hemorrhage, which caused corneal damage.

Subconjunctival Hemorrhage

This pooling of blood under the conjunctiva, typically in the inferior and temporal areas, usually does not require treatment and clears within a few weeks (*Figure 4*).[24,25] Etiologies for subconjunctival hemorrhage (SCH) include trauma (e.g., contact lens-induced in younger patients, eye rubbing, blunt injury), infections (e.g., acute hemorrhagic conjunctivitis), anticoagulation,

Valsalva maneuvers and systemic disease (e.g., hypertension, bleeding disorders).[25] SCHs may result from vascular tumors such as Kaposi's sarcoma, and cavernous hemangiomas may cause recurrent bouts in early adulthood.[24] Reports of SCHs associated with carotid cavernous fistulas exist.[26] Unexplained bilateral SCHs in a pediatric patient should flag the clinician to consider nonaccidental or accidental traumatic asphyxia, or Perthes syndrome.[27] Here, violent compression of the thorax leads to a sharp increase in venous pressure around the superior vena cava.

Contact Lens Wear

Newer materials and wear schedules have reduced the incidence of this, but contact lens use, especially in cases of excessive wear, can predispose patients to a host of red eye issues. Over-wear leads to a greater susceptibility to bacterial conjunctivitis as bacteria may accumulate in microcystic areas created by the hypoxic cornea. First-line therapy for contact lens-related red eye should be discontinuation of lens wear unless the issue was caused by a poor fit or an insertion problem.

Conjunctival hyperemia occurs in both new and established wearers. Injection is typically diffuse, circumlimbal and can have multiple etiologies, including improper fit, poor lens maintenance, non-adherence to disposal regimen and adverse reaction to a lens solution. This may lead to more severe complications such as superior limbic keratoconjunctivitis, which presents with marked injection of the superior limbus. Contact lens-induced acute red eye—an acute inflammation characterized by sudden pain and photophobia—results from overnight wear and is more likely to occur with *H. influenzae* colonization.[28] Clinicians should rule out early microbial keratitis by scanning carefully for infiltrates. Pain and photophobia frequently accompany this finding. Contact lens-induced peripheral ulceration may also present with infiltration but usually has milder symptoms.[29]

Corneal Complications

When examining the red eye patient, the entire limbus and cornea should be evaluated to determine the extent of the injection as well as to rule out any corneal lesions that may be obscured by the lids in primary

gaze (i.e., phlyctenules, infiltrates). Corneal involvement is possible in many types of conjunctivitis, with some exception to allergic conjunctivitis, and is more likely in chronic and aggressive cases. Herpes simplex keratitis can manifest in several different ways, including vesicles, dendritic ulceration, stromal keratitis and endotheliitis. An ulcerative presentation may appear daunting, but many of the same methods of a red eye examination still apply. Determining whether the ulcer is infectious guides treatment and management. Infectious ulcers tend to be larger and central, with symptoms of pain and photophobia and signs of anterior chamber reaction.

Examination of a mechanical injury, whether from an abrasion or a foreign body, should start with a pointed history to determine the nature of the incident. Similar to anterior uveitis, signs include pain, epiphora, photophobia and ciliary flush. Vital tests include lid eversion and instillation of fluorescein dye to assess the cornea and track marks. Treatment of a corneal abrasion typically involves prophylactic topical antibiotics, patching and cycloplegia until the cornea re-epithelializes. Interestingly, a study in Nepal found that 96% patients with a corneal abrasion healed without infection.[30]

Uveitis

This should always be among the top differentials in a patient presenting with acute conjunctival hyperemia. Injection is characteristically circumlimbal and engorged variably with cells and flare in the anterior chamber. Corneal findings, including keratic precipitates, typically occur in the lower half of the cornea. Suspected cases warrant a dilated exam to assess the vitreous and retina for signs or lesions suggestive of intermediate and posterior involvement.

Grading of cells and flare is important to maintain consistency, especially in practices with multiple practitioners. In these settings, consider using grading scales from the standardization of uveitis nomenclature group, which used a 1mm x 1mm slit beam to stage the number of cells and level of flare.[31] Topical corticosteroids are the mainstay of anterior uveitis treatment. The instillation interval depends on disease severity, and aggressive early therapy is common practice.

Practice Pearls

For unresolved or recurrent cases, reconsider the working diagnosis. The dilated exam can help to rule out posterior disease. Revisit the review of systems to spot any missed items or symptoms. Additional diagnostic tests such as cultures for purulent discharge, biopsies for suspected neoplasm and blood tests for sarcoidosis, thyroid or autoimmune conditions may be helpful. ■

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Dr. Williamson is the residency supervisor at the Memphis VA Medical Center.

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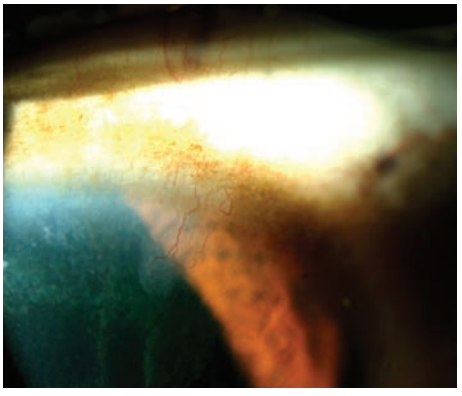

Fig. 5. Note the classic "icicle" staining pattern extending toward the pupil in this patient with limbal stem cell deficiency.

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After a clinical examination and testing, your diagnosis is confirmed. Now, it's time to develop a management plan. Here's how. **By Jessica Steen, OD, and Joseph Sowka, OD**

This month, Review of Optometry launches a new series called "Now What?" about next steps to take after confirming a diagnosis, from day one through long-term management. Each installment will cover a different chronic condition.

We are all familiar with glaucoma and the intricacies of its diagnosis. Under ideal conditions, we would like to obtain multiple intraocular pressure (IOP) readings, gonioscopy, pachymetry, optical coherence tomography (OCT) evaluation, reliable threshold perimetry, optic disc evaluation with high quality fundus photography and a detailed medical and ocular history with assessment of all risk factors. But once we have all this information—or as much of it as we can uncover—what is the next logical step? How can optometrists keep their glaucoma patients in their offices and in good health?

No one "cookbook" approach to managing glaucoma patients is possible. Every patient must be treated as an individual, and that requires some deft maneuvering from skilled clinicians. This guide is designed to give optometrists the grounding they need to know which decisions to make, and the testing protocols that can provide the basis for those decisions.

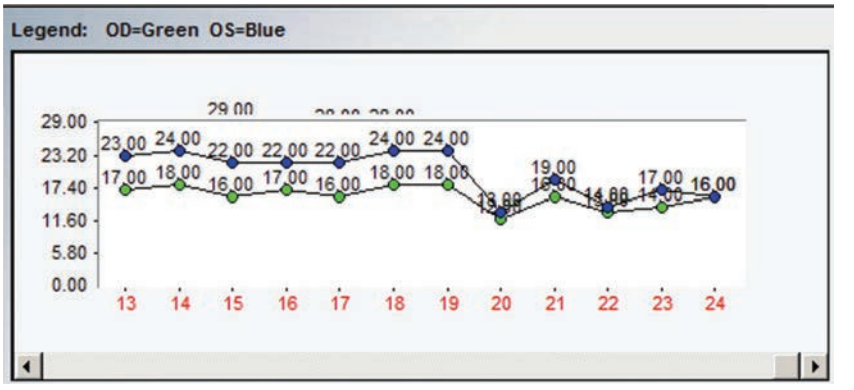

Fig. 1. This chart demonstrates an example of the importance of multiple IOP readings. At point 19, topical therapy was initiated with an apparent reduction in IOP noted at point 20. However, when assessing the entire IOP profile, it is apparent that there are post-treatment readings nearly identical to pre-treatment readings.

On the Range

When commencing glaucoma treatment, start by setting a target pressure; that is, an IOP range that best estimates the disease's impact and impact of treatment. Target IOP should be individualized, with consideration not only of the patient's maximum peak untreated IOP, but also the amount of damage that has occurred. Other relevant factors include the patient's age, life expectancy, family history, status of the fellow eye and risk of visual disability. Secondary factors such as exfoliation may necessitate a lower target IOP than primary open-angle glaucoma (POAG) due to relative severity.

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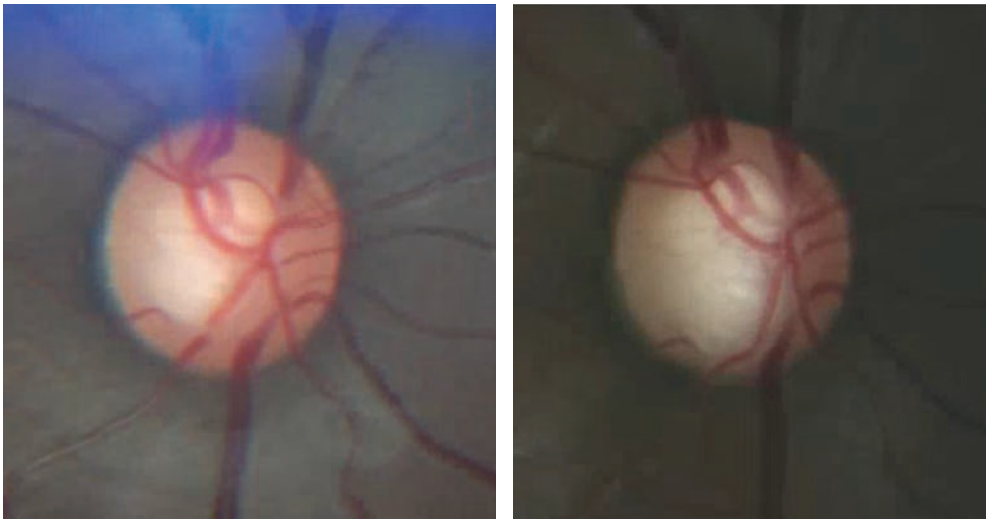

Fig. 2. This photographic comparison of a glaucoma patient's right optic disc show the baseline (at left) and one taken several years later. Note the changes in both the superior and inferior neuroretinal rim. Baseline and annual optic disc photography is an essential part of managing glaucoma patients.

With an increase in life expectancy and a general trend towards an aging population, the prevalence of ocular diseases, which tend to be more common in increased age, will also grow. More than ever, we find ourselves managing patients for an extended period—including many who are in their 80s and 90s. The treatment decisions that we make early on with a patient can impact them 30 to 40 years down the road. Though longevity is an important factor in assessing risk of visual disability, take care not to make false assumptions about how long an elderly patient is likely to live.

We typically choose an IOP range, rather than a single target number, to allow for variability. If we note progression at any point during therapy, we adjust the target downward. Typically, a 30% reduction from the peak IOP is reasonable in mild cases; however, a more aggressive reduction is often required in advanced disease to slow vision-threatening progression. In advanced disease, we feel that a 50% or greater reduction may be more appropriate. Target pressure, once set, should be adjusted throughout a patient's management. Patients who seem to have similar risk profiles for progression often progress differently, and target pressure should be adjusted to reflect this. Keep in mind that target IOP is merely a "best guess" and the patient must be monitored closely to assess disease stability.

When embarking on therapeutic pressure reduction, most practitioners opt to start medically with prostaglandin analogs (PGAs), which have a strong efficacy and safety profile.[1] This practice is so common today that there should be a reason recorded in the chart if a patient is not on a PGA (e.g., adverse effects, cost, medical contraindication).

If the patient does not achieve the target pressure with the PGA, you can consider adjunctive therapies. Topical options include beta blockers, carbonic anhydrase inhibitors, alpha-adrenergic agonists or polytherapy fixed-combination drugs. There is synergy between PGAs and these other classes, and choice is typically dictated by the patient's medical history and possible contraindications.[1]

While medication is the most common first-line therapy for newly diagnosed glaucoma patients, we do discuss selective laser trabeculoplasty (SLT) as a first-line option with our patients. Working with a patient to determine what they consider to be most important helps to determine your management plan. Those patients with mild-to-moderate disease who also have a history of intolerance with topical medications, severe corneal surface disease, difficulty with drug instillation or a preference to avoid topical therapy are suited for SLT as a first-line therapy.

General health status, patient autonomy and access to transportation may also impact your first line treatment choice. Other patient factors play a role in determining candidacy for SLT, including amount of pigment in the trabecular meshwork and angle configuration.[2] ODs should always discuss with these patients the risks and benefits of treatment and risks of any alternative approaches.

Regardless of your chosen first-line treatment for newly diagnosed patients, having the patient involved in your plan will improve adherence to the management strategy.

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Nix Monocular Drug Trials

The concept of monocular drug trials is to use the non-treated eye as a control to compare the IOP reduction in the treated eye and determine medication efficacy. In theory, this sounds like an excellent idea, but in clinical practice it isn't so simple, or as accurate, as you may think.

While IOP fluctuates, it does not fluctuate symmetrically between the two eyes, so the untreated eye is a poor control for the treated eye.[3] Also, the variability in IOP fluctuation at certain points during the day, (e.g., at 9am), is also not symmetric between the eyes. Some topical IOP-lowering medications, such as beta-blockers, can exhibit a crossover effect, lowering pressure in both eyes, even if only applied to one. This is a less of a concern with PGAs.[4] With the expansion of our knowledge of IOP fluctuations and variability, as well as drug metabolism, monocular drug trials no longer provide significant information. Once we decide that a patient needs treatment bilaterally, we initiate therapy in each eye simultaneously.

Establishing a Baseline

For glaucoma patients new to our clinic who have not yet begun IOP-lowering therapy and for whom previous records are not available, we take multiple pre-treatment IOP measurements over the course of several visits to establish true baseline, untreated peak IOP and to have a better understanding of their IOP variability, whenever possible. This is not something we would do in patients with advanced disease who've already experienced central visual field loss, but for the majority of patients, two weeks without medication is unlikely to cause clinical progression. We also try to take IOP measurements at different times of day. That is, if we typically see a patient first thing in the morning, scheduling an appointment later in the day can help to improve your understanding of a patient's IOP variability and fluctuation.

Once we initiate treatment, we do not judge efficacy based upon a single reading either. In many instances a pre-treatment IOP is similar to a post-treatment IOP. Without this knowledge, errors are likely *(Figure 1)*.

For patients newly using a PGA, have them return for a follow-up visit approximately one month after medication initiation. It can be easy to jump to a conclusion of poor response to the medication if you measure only modest reduction from baseline IOP at this first visit. Remember, IOP fluctuates. On this particular visit, maybe you caught them on an up-swing and, overall, the medication is working as you would expect it to. Don't be fooled. Therapeutic decisions should be made upon several IOP measurements. Having the patient return in another few weeks to again assess IOP—at a different time of day—will give you another important piece of information on how well a particular medication may be working, before making a treatment decision.

Staying in Control

Most practitioners will determine a patient is "well-controlled" after therapeutic IOP reduction achieves the set target. However, initially the only thing that can be truly said is that the IOP has been reduced. The term, "well-controlled" should only be used in retrospect, after the patient has been followed for a period without change. We believe in close follow-up. That is, once our initial evaluation is complete and the patient is at target, we like to assess progress every three to four months so IOP can be measured and adherence to therapy can be assessed. In low-risk ocular hypertensive patients and those with glaucoma who have remained stable over years, evaluations can be done every six months.

Evaluation of the optic nerve head should be performed at every follow-up visit. We perform an undilated optic disc evaluation with a 90D or superfield lens at each visit and perform a complete dilated fundus examination with optic disc photography once per year. The goal of optic disc examination at each visit is to observe an optic disc hemorrhage—which are easy to miss clinically, unless you're specifically looking for them. Optic disc photography is the only true way to accurately assess the optic disc for change *(Figure 2)*.

Imaging

Like optic disc photography, OCT is a valuable structural measurement that should be repeated every six to 12 months. However, the role of fundus photography and OCT is limited in advanced disease. The retinal nerve fiber layer (RNFL) is comprised of more than just axons of retinal ganglion cells—it also contains glial support cells and blood vessels, which all contribute to the RNFL's measurable thickness. Even with complete loss of axonal damage in a focal region, the measurement will never go to zero and tends to bottom out, depending on the device being used, at approximately 50µm to 55µm. After the RNFL thickness reaches approximately 55µm, even with further disease progression (which can be detected through functional measures) the structural OCT parameters will appear stable.[5]

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While gonioscopy is needed for determining the nature and mechanism of a patient's glaucoma diagnosis, it's not a one-and-done test. Gonioscopy should be periodically repeated throughout the course of management of a patient. In open-angle glaucoma patients, we typically repeat gonioscopy every two or three years, or sooner if clinical findings suggest a change. For example, if a treated patient with minimal IOP variability presents with unexpectedly elevated IOP, assess for proper therapy adherence and check the angles gonioscopically.

Secondary causes of elevated IOP include angle recession, exfoliation syndrome, pigment dispersion, peripheral anterior synechiae (PAS) or neovascularization of the angle. These can all be determined through a gonioscopic evaluation. Additionally, through the process of cataractogenesis, a patient with a previously open angle can develop a phacomorphic chronic angle closure necessitating alternate treatments.[6]

OCT can visualize the anterior chamber angle, but when assessing the anterior chamber, its significant limitations make it a useful adjunct but not a replacement for gonioscopy. In a primary angle closure suspect, OCT performed in complete darkness, without unintended indentation, may give you additional objective information about the angle structure, and may be more likely to exhibit appositional closure than gonioscopy. However, OCT does not provide information about trabecular meshwork pigmentation, the presence of PAS (although iris-trabecular meshwork contact can be observed), and dynamic observation through indentation gonioscopy cannot be performed with OCT.[7]

Facing page: **This glaucoma information sheet from the National Eye Institute (NEI) is written in easy-to-read language for patients. To download a PDF, read this article online at www.reviewofoptometry.com or scan the QR code. It can also be found on the NEI's website at nei.nih.gov/catalog/dont-lose-sight-glaucoma.**

Predicting Progression

Pachymetry should be done only once and not repeated unless there is an unusual change in the cornea such as keratorefractive surgery, trauma or degenerative disease. Pachymetry should be performed on every glaucoma patient and suspect. As a general concept, the thinner the cornea, the greater the risk for disease development.[8] However, repeated measurements are not necessary.

We like to perform threshold perimetry every six months and will reduce the frequency of testing to every 12 months if a patient shows stability over several years. While doctors and patients seem to dislike perimetry, it is a mandatory part of glaucoma management. Performing perimetry at the initial encounter and then only annually is too infrequent to properly assess for early functional progression.

The rate of progression between patients, even with seemingly similar risk profiles, varies greatly. To identify those patients who may be undergo rapid disease progression early, six visual fields performed within the first two years of diagnosis are recommended.[9] This recommendation is based on the statistical power needed to accurately identify a change in mean deviation to identify those patients most at risk for more rapid disease progression. This information enables practitioners to identify patients who may be rapid progressors and institute aggressive treatment. Once this data has been accumulated, visual fields can be performed every six months and, in cases where the patient is stable for a period of time, then annually. Due to the testing variability in perimetry, ODs should have the patient back in a month or two to repeat the test and see if the change persists and is representative of a worsening field or just one bad testing day.

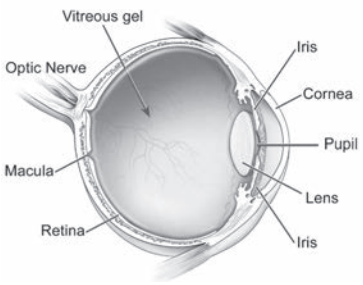
Adherence

One of the most challenging aspects to medically managing glaucoma is patient adherence to therapy.[10] Adherence to treatment through observance and persistence is mandatory, and identifying the causes of nonadherence is crucial. These factors could include the patients themselves (e.g., doubt, forgetfulness, denial), environmental factors (e.g., cost, competing activities, travel), the treatment regimen (e.g., refill, side effects, complexity) and, finally, the relationship with the clinician. Optometrists should presume that patients have low adherence to their treatment and give clear and precise information about the expected benefits of the treatment, the disease and its risks of progression.[11]

A study conducted in 2005 found that nearly half of the individuals who had filled a glaucoma prescription discontinued all topical ocular hypotensive therapy within six months, and just 37% of these individuals refilled their initial medication at three years after the first dispensing.[12] Prostaglandins are associated with better persistence and adherence than any other

1 What is glaucoma?

Glaucoma is a group of diseases that can harm the optic nerve and cause vision loss or blindness. The optic nerve is a bundle of nerves that carry messages from the eye to the brain. The most common form of glaucoma is primary open-angle, which this brochure is about.



2 What causes glaucoma?

At the front of the eye, there is a small space where clear fluid flows in and out. This clear fluid feeds nearby eye tissue. When the clear fluid flows too slowly, it creates pressure on the optic nerve. This pressure can harm the optic nerve and cause glaucoma and vision loss.

3 Who is most likely to get glaucoma?

Anyone can get glaucoma, but some people have a higher chance of getting it. People who have a higher chance are African Americans over the age of 40 and anyone over the age of 60 (especially Mexican Americans). If glaucoma runs in your family, you also have a higher chance of getting it.

Normal vision.

A scene as it might be viewed by a person with glaucoma.

4 What are the symptoms of glaucoma?

In its early stages, many times there are no symptoms or pain. As glaucoma gets worse, you may slowly lose your side vision. If it remains untreated, you may miss objects to the side and out of the corner of your eye. It is like looking through a tunnel. Over time, straight-ahead vision may decrease until no vision remains.

5 How do you know if you have glaucoma?

An eye care professional can tell if you have glaucoma by giving you a comprehensive dilated eye exam. During the exam, drops are placed in your eyes to widen, or dilate, the pupils. Then a special lens is used to look at the optic nerve for damage. After the exam, your close-up vision may be blurry for a period of hours. You may also have a visual field test to check for changes in your side vision.

6 How can glaucoma be treated?

Glaucoma cannot be cured, but it can be treated to keep it from getting worse. Catching it early is key to protecting your vision. Eye drops and medicine can help your eyes make less fluid or can help drain the fluid from the eye properly. Laser surgery can also make it easier for fluid to leave the eye. Regular surgery can make a new space where the fluid can drain.

7 What can you do to protect your vision?

Get a comprehensive dilated eye exam at least once every two years. This is more important if you are African American over age 40; are over age 60, especially if you are Mexican American; or have a family history of glaucoma. Finding and treating glaucoma early can help keep the disease from getting worse and reduce your risk of vision loss.

Medicare will help pay for an annual dilated eye exam for some people at high risk for glaucoma. This includes people with diabetes, people with a family history of glaucoma, and African Americans age 50 and older.

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drug class. Furthermore, patients with diagnosed glaucoma were more likely to adhere to therapy than patients with merely suspect glaucoma. Education about glaucoma and the potential visual disability has been shown to enhance therapeutic adherence.[12]

We have found that the best way to enhance medical therapy adherence is through repeated education to the patient and any family members about glaucoma and the visual consequences of not adhering to treatment. Providing written material explaining the disease in patient-friendly language is invaluable. While doctors can create their own specific written messages, we typically employ glaucoma information sheets made available by pharmaceutical companies. These brochures are very well done, readily available and are not product-promotional in any way (except for perhaps a small company logo). We obtain these directly from drug companies and their representatives and find them invaluable in our patient education.

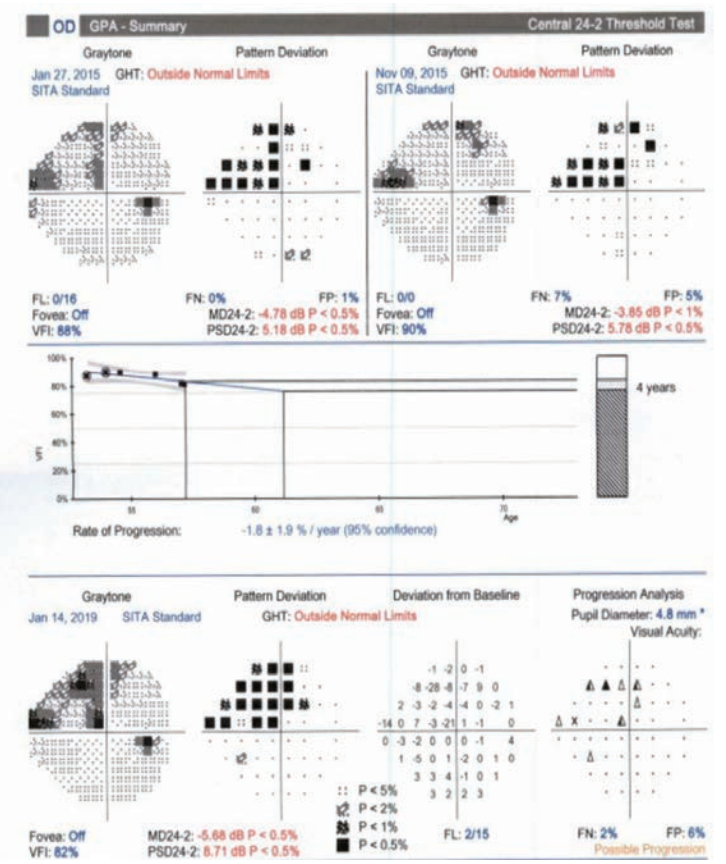

Fig. 3. Proper periodic repetition of threshold perimetry allows clinicians to employ a guided progression analysis to determine if glaucoma has progressed and at what rate the progression has occurred.

Better? Or Worse?

Differentiating clinically relevant progression from inherent variability and fluctuation is one of the biggest challenges in managing glaucoma patients. While some identifiers of progression, such as upward trending IOP, above your target pressure, optic disc hemorrhage, new wedge or nerve fiber layer defects are relatively objective. Assessing progression using adjunctive tests such as OCT and visual fields can be more challenging. Other factors tend to muddy the waters of progression identification further—the amount of baseline damage, the patient's age and IOP may all have different relative weights in your threshold for determining clinically relevant progression.

While optometry has not identified a single standard for identifying progression, a combination of functional, structural and clinical data contribute to the identification of clinically meaningful change.

While most patients with glaucoma progress slowly, those who may progress quickly are at significant risk of vision loss, even with treatment, and it's necessary to identify them early. This can be achieved with OCT, perimetry systems, progression analysis software, visual field and OCT RNFL evaluation.[13]

Progression analysis software removes the ambiguity of a normative database and compares RNFL thickness of a patient to their own baseline to determine change over time. This means that the raw baseline images for every patient should be checked to ensure that they are of good quality, well-centered, without missing data points, and that the automated segmentation has been performed correctly; otherwise, with an inaccurate baseline, true progression may be masked or true stability may appear as progression. Also, if you're performing multiple scans of the same type on the same day, delete the poorer quality images; otherwise, the device will automatically include the scan, which was performed first in the progression analysis.

When analyzing the guided progression analysis information, keep in mind that some age-related decrease in RNFL is expected.[14] Typically, a change of 10µm of average RNFL thickness (or at

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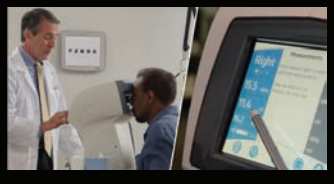

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least twice the inherent variability in measurement) is recommended before considering real change as a possibility.[15] Proprietary differences in imaging software between manufacturers exists, so if you are imaging a patient on different instruments of different manufacturers, while the general trends of data is valuable, direct RNFL and GCC thickness parameters cannot be directly compared between instruments.

While structural tests such as OCT do not require patient input, they are still subject to measurement errors and inconsistencies that can lead to perception of progression in the absence of real change. Functional evaluation, using visual field analysis, is a mainstay of glaucoma management and key data to incorporate when determining if a patient may be progressing. Amassing a number of reliable visual fields is essential to employ a guided progression analysis to determine if change is not only taking place but also the rate at which the progression is occurring *(Figure 3)*.

Individualize Care

In general, most patients seek care when they have a specific problem—with their goal being improvement of that problem with treatment. However, managing glaucoma requires a shift in our patient's understanding of the typical 'problem-prescription-cure' algorithm. The clinician's goal in managing patients with glaucoma, which is central for patients to understand, is not to cure the condition or improve functionality or quality of life—but instead to prevent functional decline or to prevent reduced quality of life. This isn't the same thing as simply lowering the IOP, or preserving the nerve fiber layer—over-prescribing can be just as harmful as under-prescribing. Adverse effects and the significant impact of the cost of medications all impact a patient's quality of life.

Quality of life as it relates to glaucoma describes the feeling or perception that the patient has about how they are functioning. For example, if a patient has a paracentral defect, which has slowed their reading speed, how does she feel about this change? For some patients this may be a minor inconvenience, but for others, this may have a drastic impact on their quality of life. Along the same line, take patient concerns seriously. If that same patient reports that she has been having worsening difficulty reading, consider that this change could be related to disease progression. In this case, a 10-2 visual field may highlight a deepened paracentral defect, which may result in a change in therapy.

Simply asking a patient how they're feeling and managing with their medications, especially when patients may be facing functional vision loss, can go a long way. Although we're not professional counselors, identifying when a patient may be having difficulty dealing with vision loss and recommending that they discuss these challenges with their primary care doctor or with a counselor while arranging for low vision services can have a significant impact on a patient's well-being.

Despite our growing understanding of the complex pathophysiology of glaucoma, we still only have one option to slow disease progression—reducing the pressure. Luckily, we have a number of pharmaceutical options to accomplish that, but their use must be paired with proficient clinical acumen. This means navigating the patient's risk factors for progression, setting a target pressure range and being ready to change that initial target by monitoring changes using available technology. ■

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Dr. Sowka is chief of advanced care and director of the glaucoma service at Nova Southeastern University College of Optometry.

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CAN YOU SPOT THESE RETINAL VASCULAR ABNORMALITIES?

These findings are closely linked with underlying systemic conditions—impacting both the physical and ocular health of the patient.

By Nick Fogt, OD, PhD, and Theresa Watt, BS

The retinal vasculature provides clinicians the unique opportunity to directly and noninvasively evaluate changes in the eye that reflect the systemic health of the patient. Classic examination techniques such as direct and indirect ophthalmoscopy, in addition to developed and newly developing retinal imaging devices, allow optometrists to detect subtle changes in retinal vasculature.

Here's a summary of the relationships between changes in systemic health and the retinal vasculature.

Basic Retinal Vascular Anatomy

To properly navigate abnormal retinal vasculature, it's helpful to first review the normal retinal vascular anatomy:

• ***Retinal blood supply.*** The retinal blood supply is provided by the central retinal artery (CRA) and the choroidal blood vessels.[1] These two systems originate from the ophthalmic artery, which branches from the internal carotid artery. The inner retinal layers are nourished by the CRA, which courses along the boundary of the optic nerve sheath and enters via the optic nerve head. The other sources of blood supply are the choroidal vessels, which originate from the posterior ciliary artery branches of the ophthalmic artery to supply the outer retinal layers.

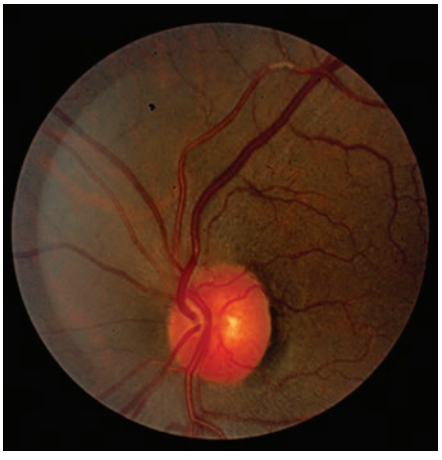

Fig. 1. Increased reflectivity from the arteriole vessel wall and vascular tortuosity.

As the CRA projects though the optic nerve, the artery divides to form superior and inferior branches. Subsequently, these branches divide into the superior nasal and superior temporal arteries and the inferior nasal and inferior temporal arteries, serving the four quadrants of the retina.[1,2] The extensive arterial network progressively branches until arriving at the ora serrata. The retinal venous circulation also has branches in these four quadrants, and these venous branches ultimately drain into the central retinal vein, which leaves the eye in the optic nerve.

In about 70% of arteriovenous (AV) crossings, the arteriole is "on top" (that is, on the vitreal side) of the venule.[3] The arteriole and venule share a common adventitial sheath at these crossings. Branches from the central retinal vessels form capillary layers in the nerve fiber layer, ganglion cell layer and the inner nuclear layer. The outer plexiform and photoreceptor layers contain no blood supply from the

CRA branches and are therefore nourished by the choroid.

About 15% to 20% of individuals possess a cilioretinal artery derived from the short posterior ciliary arteries, which courses toward the fovea and augments the retinal vasculature between the optic nerve head and the macula.[1]

• ***Choroidal blood supply.*** The choroidal vessels are derived from the ophthalmic arteries.[4] The major branch of the internal carotid divides into the left and right ophthalmic arteries. The ophthalmic arteries extensively branch into the posterior ciliary arteries as they advance toward the globe.

Further branching gives rise to the short posterior ciliary arteries supplying the posterior choroid and the long posterior ciliary arteries, which nourish the anterior portion of the choroid.

The short posterior ciliary arteries also branch into the choriocapillaris. From the choroid, venous circulation exits the eye through the vortex veins in each quadrant of the retina. The vortex veins drain into the superior and inferior ophthalmic veins, which leave the eye and enter the cavernous sinus.

General Vascular Pathophysiology

Abnormal changes in the retinal vasculature are closely tied to underlying systemic conditions.[5-15] Some important risk factors for alterations in the retinal vasculature include diabetes, hypertension, hyperlipidemia, smoking, obesity and sedentary lifestyle. The likelihood of encountering these vascular changes increases with age.

Systemic vascular abnormalities bring about vascular remodeling.[16,17] In this process, changes in hemodynamic conditions result in alterations of the vasculature. These alterations may include changes in vessel diameter, changes in the diameter of the vessel lumen, thickening of the vessel wall (which can result in a decrease in vessel lumen diameter) or atherosclerosis (with a subsequent reduction in luminal diameter).

Disruption of the blood-retinal barrier may ultimately occur, resulting in vascular leakage including hemorrhages, hard exudates and edema.

Atherosclerosis develops from a buildup of plaques on the lumen of vessel walls. This occurs in response to uncontrolled diabetes, hypertension, hypercholesterolemia and many other systemic disorders.

Traditionally, the development of atherosclerotic disease was described in terms of endothelial cell damage, which led to smooth muscle proliferation and then deposition of low-density lipoproteins (LDL) to the lumen walls.[16] More recently, inflammation is recognized as a major contributor to atherosclerosis.[18] As deposition of material increases, hard plaques increase in thickness and present an emergent risk of thrombus formation. Rupture of these plaques or thrombi can lead to stroke and increased mortality.

While atherosclerosis is described as a risk factor in some of the discussion below, remember that the atherosclerotic process is often accompanied by an underlying systemic disease.

Specific Retinal Vascular Abnormalities

Highlighted below are characteristic retinal changes that are important to recognize:

• ***Tortuosity.*** This vascular anomaly can be seen in both retinal

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Estimated Time to Complete Activity: 2 hours

Jointly provided by Postgraduate Institute for Medicine (PIM) and RGVCE

Educational Objectives: After completing this activity, the participant should be better able to:

- Evaluate ocular signs, symptoms and pathophysiology of retinal vascular abnormalities.
- Identify changes in retinal vascular architecture, such as increased retinal vein caliber, retinal vascular tortuosity, increased prominence of the retinal arterial reflex, venous nicking, "copper" or "silver wire" appearance, as well as the detection of cholesterol, calcium or thrombotic emboli.
- Provide management, additional testing or referral to prevent vision loss and possible systemic impairment.
- Offer patient education regarding potential retinal, systemic, neurological and cerebral vascular morbidities and risks.

Target Audience: This activity is intended for optometrists engaged in the care of patients with retinal vascular abnormalities.

Accreditation Statement: In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and RGVCE. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education, the Accreditation Council for Pharmacy Education, and the American Nurses Credentialing Center, to provide continuing education for the healthcare team. Postgraduate Institute for Medicine is accredited by COPE to provide continuing education to optometrists.

Faculty/Editorial Board: Nick Fogt, OD, PhD, associate professor, Illinois College of Optometry, and Theresa Watt, BS.

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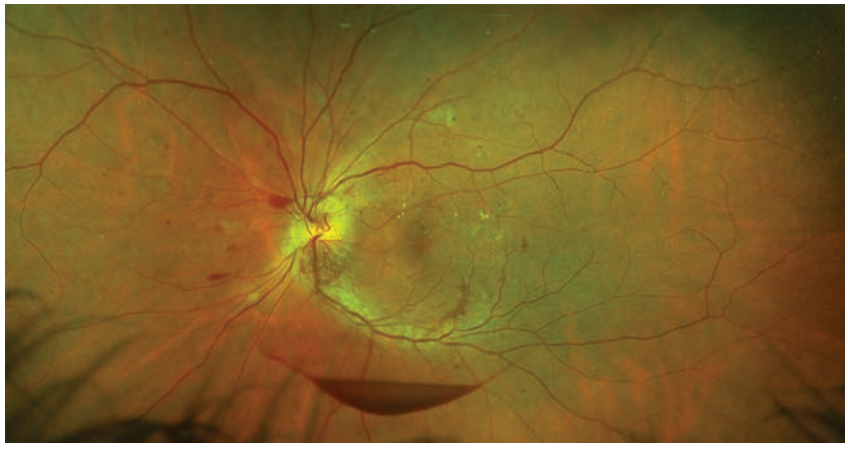

Fig. 2. Proliferative diabetic retinopathy with intraretinal hemorrhages, a preretinal hemorrhage and hard exudates.

arteries and veins and their successive branches (*Figure 1*). Systemic vascular diseases can alter the stability of blood vessel walls, which then results in changes in the course or shape of the vessels.[11] In terms of systemic vascular diseases, retinal vascular tortuosity is primarily associated with hypertension and atherosclerosis.

• ***Changes in vessel caliber.*** Dilated retinal venules (perhaps associated with increased retinal venous pressure) and narrowed retinal arterioles (perhaps due to vessel attenuation associated with high lumen pressure) may occur and are potentially associated with a number of ocular and systemic disorders as described below.[10]

• ***Retinal hemorrhages.*** Breakdown of the blood-retinal barrier can lead to blood leakage (*Figure 2*). These hemorrhages can present in a multitude of appearances and may occur anywhere within the retina.[8,19] Dot-and-blot hemorrhages are small, often circular in appearance and can be found in the inner nuclear and outer plexiform layers of the retina. Flame-shaped hemorrhages follow the course of the nerve fiber layer and may have a splinter-like appearance. Hemorrhages may also appear in the preretinal (between the internal limiting membrane and the nerve fiber layer) and subhyaloid (between the internal limiting membrane and the posterior boundary of the vitreous) spaces. These latter hemorrhages may present with a boat-shaped appearance. Vitreous hemorrhages may also occur.

• ***Widening of the arterial light reflex.*** This emanates from the junction between the blood column and the retinal arterial wall. A wider reflex manifests as a result of wall thickening/hardening due to persistent sclerosis, or perhaps as a result of reduction in the velocity of blood flow through the vessels (*Figure 1*).[7] Chronic hypertension is one of the main culprits for this presentation, which researchers describe as a "copper" or "silver wire" appearance. When the reflex has a red-orange hue, this is referred to as copper wiring. Silver wire vessels give a white reflection from advanced sclerotic sheathing surrounding the arterial wall. In one study, severe enhancement of the arterial light reflex was associated with high blood pressure.[7] However, the same study found no relationship between an enhanced arterial light reflex and mortality rate.[7]

• ***Emboli.*** These may travel to the retinal vasculature (*Figure 3*). Emboli are potentially composed of cholesterol, calcium and platelet-fibrin. Cholesterol emboli often appear as highly reflective, small, bright yellow or white spots within retinal vessels and are associated with atherosclerotic disease that includes the carotids.[20] Calcific emboli appear as larger white deposits and typically are released from calcified heart valves.[21] Platelet-fibrin emboli are less reflective, dull white-grey deposits.[22] Talc retinopathy is another embolitic finding, predominantly caused by injected illicit drug use that had talc as a filler agent.[23]

• ***Arteriovenous crossing changes.*** Due to the typical anatomical position of arteries overlaying veins in the retina, changes in blood vessel wall cellular composition can create a "banking" or "nicking" appearance at arteriovenous crossings. This is due to arterial compressive impingement on the surface of the veins, as the arteries and veins share an adventitial sheath at these crossings.[3]

• ***Neovascularization.*** Also referred to as angiogenesis, neovascularization is the anatomical growth of new blood vessels due to hypoxic conditions. Oxygen-deprived tissue results in increased levels of various platelet and vascular endothelial growth factors (VEGF).[24] These initiate the development of abnormal and fragile blood vessels in this area.

Pathophysiology of Diabetes and Hypertension

Because diabetes and hypertension are commonly encountered in clinical practice, some details related to the pathophysiology of these disorders are discussed here:

• ***Diabetes.*** Increased blood glucose levels contribute to lipid

deposition in vessels walls, ultimately resulting in atherosclerotic vascular changes and decreased perfusion to the retina. Primary changes in retinal vasculature due to diabetes include reduction in pericytes in the retinal capillaries and vascular cell apoptosis leading to impaired blood supply to the retina. Natural mechanisms then upregulate angiogenic factors such as VEGF to generate new vascular supplies to the retina. However, these neovascular vessels are prone to leakage.[25] Vision loss may ensue from bleeding, edema or epiretinal membrane (ERM). Major risk factors for diabetic retinopathy are duration of diabetic diagnosis and blood glucose control.[26] Diabetic patients with hypertension also show reduced diabetic retinopathy progression when blood pressure is tightly controlled.[2]

• ***Hypertension.*** Chronically elevated blood pressure can also lead to atherosclerotic changes in the retinal vasculature. Normal blood pressure is defined as a systolic pressure less than 120mm Hg and a diastolic pressure less than 80mm Hg.[27,28] Hypertension is associated with endothelial cell damage and deterioration of arteriole smooth muscle.[29,30] Destruction of the vessels walls is followed by plasma leakage and vascular necrosis.[31] The resultant narrowing of the vascular lumen leads to systemic ischemic events, and in the eye promotes vascular infarcts (cotton-wool spots) and vascular leakage (hemorrhage, hard exudate, edema). The major risk factors for hypertensive retinopathy are the duration of hypertension and the level of blood pressure elevation.[32]

Retinal Vascular Changes and Systemic Health

Several conditions other than diabetes and hypertension can also affect the retina:

• ***Metabolic syndrome.*** This involves a group of five risk factors that include a large waistline (abdominal obesity), a high triglyceride level, a low high-density lipoprotein (HDL) level, high blood pressure and high fasting blood glucose. A person with three or more of these risk factors is diagnosed with metabolic syndrome. The risk factors associated with metabolic syndrome promote the development of atherosclerotic disease (at least partially by activating immune responses); as the number of these risk factors increases, the risk for coronary heart disease, stroke and diabetes also increase.[33]

Not surprisingly, retinal vascular changes that are potentially associated with risk factors for metabolic syndrome have also been associated with risk for coronary heart disease and stroke. This is not to say that risk factors for metabolic syndrome are the only factors associated with these vascular changes, but rather that clinicians should be aware that the combination of risk factors associated with metabolic syndrome may result in additive systemic and ocular effects.

• ***Narrowed retinal arterioles and larger retinal venules.*** Narrowed arterioles and larger venular diameters (which are linked with higher levels of systemic inflammation and vascular endothelial cell dysfunction) have been associated with the risk for coronary heart disease in a number of studies.[10]

For instance, the Atherosclerosis Risk in Communities (ARIC) Study demonstrated that lower arteriole-to-venule (AVR) ratios were predictive of coronary heart disease in women but not in men.[34] A recent report from the ARIC group concluded that narrower retinal arterioles and wider retinal venules are associated with greater risk of mortality and stroke in men and women and a greater risk for coronary heart disease in women.[35] An analysis of combined data from the Blue Mountain Eye Study and the Beaver Dam Eye Study concluded that both narrower arterioles and wider venules are predictive of higher risk for mortality associated with coronary heart disease and stroke in people between 43 to 69 years old.[36] A meta-analysis also demonstrated an association between narrowed retinal arterioles and dilated retinal venules and coronary heart disease in women but not in men.[37]

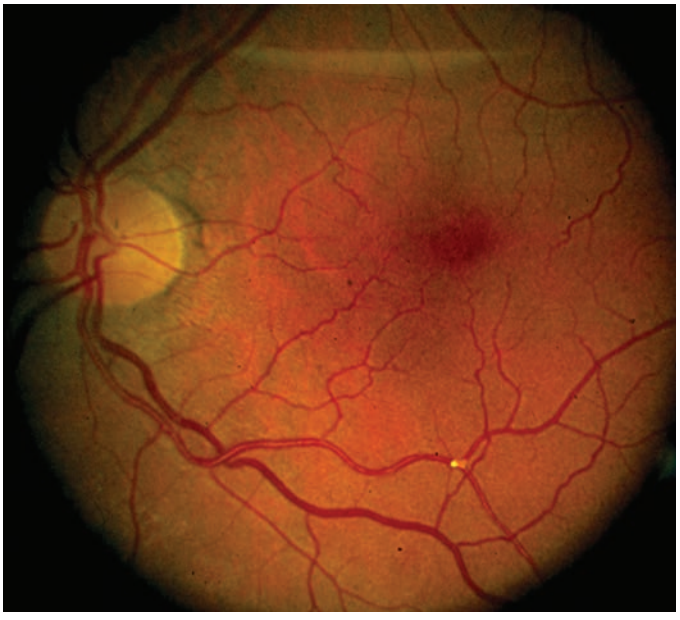

Fig. 3. Retinal embolus with vascular tortuosity.

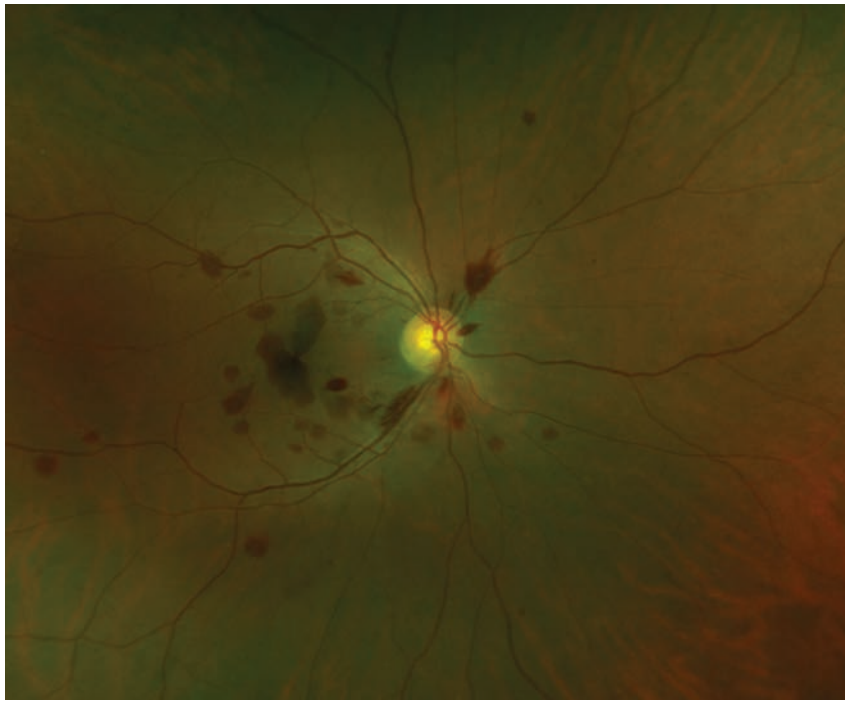

Fig. 4. Central retinal vein occlusion associated with systemic hypertension.

Some researchers have suggested that quantifying the AVR can be useful in classifying patients for their future risk of cardiovascular events, although the impact in clinical practice of assessing the AVR ratio for stratifying patients for cardiovascular risk may be relatively modest.[10,35,38] In any event, the AVR ratio can certainly be useful for eyecare practitioners to assess the presence and perhaps the extent of systemic cardiovascular disease.

• ***Microvascular findings.*** Other vascular changes associated with systemic disorders may also be predictive of coronary heart disease. One such group of findings is arteriovenous crossing changes (e.g., nicking and banking) and arteriolar narrowing. A second group is those associated with retinopathy, including microaneurysms, vascular leakage (hemorrhage or lipid exudate) or vascular blockage (cotton-wool spot) and neovascularization. The results of a study examining cases from the Beaver Dam Eye Study (ages 43 to 84) showed that retinopathy (including microaneurysms, intraretinal hemorrhages, hard exudates, cotton-wool spots, venous beading, intraretinal microvascular abnormalities, neovascularization, preretinal hemorrhages and vitreous hemorrhages) was related to cardiovascular mortality, while only middle-aged persons showed associations with other retinal findings (arteriovenous crossing changes and arteriolar narrowing) and cardiovascular risk.[6]

• ***Retinal arteriolar emboli.*** These are associated with the risk of future cardiovascular events, particularly stroke.[39] These emboli may be derived from cardiac plaques or carotid artery plaques. Research shows hypertension, diabetes and cigarette smoking may all be associated with incident retinal emboli.

Because retinal emboli may be associated with systemic and ocular risks (i.e., retinal artery occlusion), patients with asymptomatic retinal emboli should be referred to a physician for a cardiovascular workup shortly after the ocular examination.

Cardiovascular and Cerebrovascular Events

Specific retinal vascular disorders can also be related to cardiovascular or cerebrovascular complications:

• ***Hypertension and hypertensive retinopathy.*** We can use a three-grade classification scheme as proposed by researchers to categorize hypertensive retinopathy.[8,40] The first grade is mild hypertensive retinopathy, which is characterized by changes in the arteriolar walls including widening of the arterial light reflex, arteriolar narrowing and arteriovenous crossing changes. The second grade, moderate hypertensive retinopathy, includes microaneurysms, vascular leakage (hemorrhages and hard exudates) and vascular occlusion (cotton-wool spots). The third grade, severe hypertensive retinopathy, includes any, or all, changes in moderate hypertensive retinopathy in addition to optic disc edema.

The choroid may also be affected by hypertension.

Moderate hypertensive retinopathy and to a lesser degree mild hypertensive retinopathy are associated with an increased risk for stroke. Hypertensive retinopathy may even be related to cardiac disease. Patients with findings of hypertensive retinopathy should have their blood pressure checked in the office and should be referred for a cardiovascular workup and treatment for their hypertension.

Hypertension can also predispose patients to retinal venous occlusions and retinal artery occlusions. Retinal vascular occlusions are the second most common sight-threatening retinal vascular disorder (diabetic retinopathy being the most

common).[15] While hypertension and hyperlipidemia are common systemic associations with vascular occlusion, many other potential systemic associations, including diabetes, atherosclerotic disease and hypercoagulation disorders exist.[9,14] Certain classes of medications can also predispose patients to retinal venous occlusions.[14]

In retinal vein occlusions, the veins in the pre- and post-venous occlusion phases are often dilated and tortuous (*Figure 4*).[8,41] Retinal hemorrhages are characteristic of retinal vein occlusions, and cotton-wool spots may appear. Post-venous occlusion changes in the retinal vasculature may include vascular sheathing and retinal or optic nerve head collateral vessels.

Management of retinal venous occlusions involves addressing the likely systemic factors underlying the occlusion and consulting with an ophthalmologist regarding the potential for macular edema, retinal neovascularization or, in some cases, iris neovascularization.

Retinal artery occlusions often result from emboli originating from the carotid artery or the heart. These occlusions are associated with a number of systemic risk factors in addition to carotid artery disease, such as hypertension, atherosclerosis, heart abnormalities and many hematologic and inflammatory issues.[8] It is important to determine whether an arteritic inflammatory disorder is associated with the vascular occlusion.

Central retinal artery occlusion is a true ocular emergency, requiring immediate care in an attempt to restore circulation to the eye, although the efficacy of treatments (e.g., paracentesis, intraocular pressure-lowering drugs) is unclear.[42] Branch retinal artery occlusion may be treated in a similar manner as central retinal artery occlusion, but carries a better visual prognosis.[43,44]

Recently, researchers have suggested that transient monocular vision loss attributable to vascular causes, branch retinal artery occlusion, and central retinal artery occlusion be grouped together under the term "acute retinal arterial ischemia."[45] In addition, acute retinal arterial ischemia has now been characterized as equivalent to stroke in the brain. Researchers recommend that all of these entities be managed in the same way. Specifically, once any of these disorders is diagnosed, the patient should be referred to an emergency department associated with a stroke center. This is because patients with these disorders are at significant risk for stroke and cardiac events, and the risk of these things occurring rises with delays in treating those issues (e.g., carotid stenosis, cardiac abnormalities) that lead to such events.[45] In fact, the incidence of stroke is highest in the first week after a central retinal artery occlusion and remains high over the first 30 days after the occlusion.[46]

• ***Diabetes and diabetic retinopathy.*** In patients with both Type 1 and Type 2 diabetes, the presence of diabetic retinopathy is often associated with both neuropathy and kidney disease (albuminuria).[47] The extent of diabetic retinopathy can therefore be taken as an indicator of the extent of systemic microvascular disease. Further, a literature review suggested that higher rates of all-cause mortality were found in Type 1 and Type 2 diabetic patients with diabetic retinopathy compared with diabetic patients without diabetic retinopathy.[48] The relative risk was higher in patients with proliferative diabetic retinopathy compared with patients with nonproliferative diabetic retinopathy. Diabetic retinopathy was also associated with an increased risk of stroke and heart failure.

• ***Ocular ischemic syndrome.*** This occurs due to stenosis of the carotid artery (or rarely the ophthalmic artery) and subsequent reduction (hypoperfusion) of blood flow to the eye.[12]

Changes in the anterior and posterior segments may occur in ocular ischemic syndrome. In terms of vascular changes in ocular ischemic syndrome, laterality is a significant feature to consider. Ocular ischemic syndrome tends to be unilateral, while diabetic retinopathy tends to be bilateral. In ocular ischemic syndrome, the retinal veins may be dilated and non-tortuous, while the arteries may be narrowed. Retinal hemorrhages, particularly in the mid-periphery, may exist, along with microaneurysms in the mid-periphery and in the posterior pole.[12,49] Macular capillary telangiectasias may also appear. Neovascularization of the retina is possible, and iris neovascularization is common.[49]

Ocular ischemic syndrome is caused primarily by atherosclerotic disease. The most common underlying systemic causes of atherosclerotic disease that lead to ocular ischemic syndrome are hypertension and diabetes. There is a high, five-year mortality rate associated with ocular ischemic syndrome, primarily related to cardiovascular disease and stroke.[12] Thus, patients who manifest ocular ischemic syndrome should be referred for a cardiac and carotid evaluation.

Abnormal vascular findings in the retina are often harbingers of systemic disease that could lead to vascular events such as stroke. All of the retinal findings discussed here should prompt clinicians to refer patients for a systemic cardiovascular workup and discuss

modifiable risk factors with the patient, such as smoking cessation and reduction in body mass index, perhaps through a combination of diet and exercise. ■

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1. In approximately what percentage of arteriovenous crossings in the retina does the arteriole lie closer to the vitreous than the venule?
a. 10%.
b. 30%.
c. 70%.
d. 95%.

2. Which best describes the percentage of people with a cilioretinal artery?
a. 3% to 5%.
b. 15% to 20%.
c. 60% to 70%.
d. 90% to 95%.

3. Which hemorrhage is most likely to present with a boat-shaped appearance?
a. Flame-shaped retinal hemorrhage.
b. Preretinal and subhyaloid hemorrhage.
c. Dot or blot intraretinal hemorrhage.
d. Vitreous hemorrhage.

4. Which is true regarding widening of the arterial light reflex?

a. Reduction in the velocity of blood flow through the vessels has been suggested as a mechanism for widening of the arterial light reflex.
b. Copper wiring of the vessels is associated with a white reflection.
c. Silver wiring of the vessels is associated with a red-orange reflection.
d. There are no systemic associations with changes in the arterial light reflex.

5. Which of the following best describes retinal emboli?
a. Cholesterol emboli are often highly reflective.
b. Calcific emboli are typically the most reflective emboli.
c. Platelet-fibrin emboli are bright white.
d. Retinal emboli are always derived from the carotid artery.

6. Which is true regarding risk factors for retinopathy?
a. Blood pressure control has no effect on diabetic retinopathy.
b. Duration of diabetes is a major risk factor for diabetic retinopathy.
c. Blood glucose control has no effect on diabetic retinopathy.
d. Level of blood pressure elevation has no effect on hypertensive retinopathy.

7. Which blood pressure reading is within the normal range?
a. 200/150mm Hg.
b. 150/100mm Hg.
c. 135/95mm Hg.
d. 115/75mm Hg.

8. All of the following are considered a risk factor for metabolic syndrome, *except*:
a. Abdominal obesity.
b. High triglyceride level.
c. High fasting blood glucose level.
d. High HDL level.

9. Specific systemic diseases resulting from the risk factors in metabolic syndrome include all of the following, *except*:
a. Coronary heart disease.
b. Stroke.
c. Diabetes.
d. Large waistline.

10. The acronym ARIC represents which study cited in the article?
a. Arteriosclerotic Risk in Communities Study.
b. Atherosclerosis Risk in Communities Study.
c. Age-related Risk in Communities Study.
d. All-cause Risk in Communities Study.

11. Analyses from the ARIC study, and from combined data from the Blue Mountain Eyes Study and the Beaver Dam Eye study, concluded the following, at least for some groups of patients:
a. Wider arterioles and wider venules are predictive of coronary heart disease.
b. Wider arterioles and narrower venules are predictive of coronary heart disease.
c. Narrower arterioles and wider venules are predictive of coronary heart disease.
d. Narrower arterioles and narrower venules are predictive of coronary heart disease.

12. In a study examining cases from the Beaver Dam Eye Study, all of the following were features of the study, *except*:
a. Retinopathy was related to cardiovascular mortality.
b. All persons in the study showed associations between retinal findings, such as arteriolar narrowing, and cardiovascular risk.
c. Retinopathy findings included presentations such as microaneurysms and hemorrhage.
d. Retinal findings, such as arteriovenous crossing changes and arteriolar narrowing, were compared with cardiovascular risk.

13. Regarding retinal emboli, all of the following are true, *except*:
a. Patients with asymptomatic retinal emboli require a cardiovascular workup.
b. Hypertension has been associated with incident retinal emboli.
c. Diabetes has been associated with incident retinal emboli.
d. Cigarette smoking has not been associated with incident retinal emboli.

14. Which best describes the three-grade classification scheme for hypertensive retinopathy?
a. Mild hypertensive retinopathy—vascular leakage.
b. Moderate hypertensive retinopathy—vascular leakage.
c. Severe hypertensive retinopathy—optic disc edema only.
d. Moderate hypertensive retinopathy—optic disc edema.

15. Which best describes the relationship between hypertensive retinopathy and systemic vascular diseases?
a. Mild hypertensive retinopathy is not associated with an increased risk of stroke.
b. There is clearly no relationship between hypertensive retinopathy and cardiac disease.
c. Moderate hypertensive retinopathy is associated with an increased risk of stroke.
d. Hypertension is an uncommon association with retinal venous occlusions.

16. Which is the most common sight-threatening retinal vascular disorder?
a. Moderate hypertensive retinopathy.
b. Branch retinal vein occlusion.
c. Branch retinal artery occlusion.
d. Diabetic retinopathy.

17. All of the following are potential findings associated with a retinal vein occlusion, *except*:
a. Retinal hemorrhages.
b. Cotton-wool spots.
c. Dilated, tortuous retinal arterioles.
d. Macular edema.

18. Regarding diabetes, all of the following have been reported, *except*:
a. The extent of diabetic retinopathy is an indicator of the extent of systemic microvascular disease.
b. The relative mortality risk has been reported to be higher for patients with nonproliferative diabetic retinopathy compared with patients with proliferative diabetic retinopathy.
c. Diabetic retinopathy has been associated with an increased risk for stroke.
d. Diabetic retinopathy has been associated with an increased risk for heart failure.

19. All of the following are common features of ocular ischemic syndrome, *except*:
a. Bilaterality.
b. Mid-peripheral hemorrhages.
c. Dilated, non-tortuous veins.
d. Anterior and posterior segment changes.

20. All of the following are associated with ocular ischemic syndrome, *except*:
a. Cardiovascular disease.
c. Stroke.
b. Atherosclerotic disease.
d. Low five-year mortality rate.

Examination Answer Sheet

Can You Spot These Retinal Vascular Abnormalities?

Valid for credit through March 15, 2022

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Salus University has sponsored the review and approval of this activity.

Processing: There is a four-week processing time for this exam.

Answers to CE exam:

1. Ⓐ Ⓑ Ⓒ Ⓓ
2. Ⓐ Ⓑ Ⓒ Ⓓ
3. Ⓐ Ⓑ Ⓒ Ⓓ
4. Ⓐ Ⓑ Ⓒ Ⓓ
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19. Ⓐ Ⓑ Ⓒ Ⓓ
20. Ⓐ Ⓑ Ⓒ Ⓓ

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives:
1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent

21. Evaluate ocular signs, symptoms and pathophysiology of retinal vasculature abnormalities. ① ② ③ ④ ⑤

22. Identify changes in retinal vascular architecture, such as increased retinal vein caliber, retinal vascular tortuosity, increased prominence of the retinal arterial reflex, venous nicking, "copper" or "silver wire" appearance, as well as the detection of cholesterol, calcium or thrombotic emboli. ① ② ③ ④ ⑤

23. Provide management, additional testing or referral to prevent vision loss and possible systemic impairment. ① ② ③ ④ ⑤

24. Offer patient education regarding potential retinal, systemic, neurological and cerebral vascular morbidities and risks. ① ② ③ ④ ⑤

25. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)
Ⓐ I do plan to implement changes in my practice based on the information presented.
Ⓑ My current practice has been reinforced by the information presented.
Ⓒ I need more information before I will change my practice.

26. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number): ☐

27. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

ⓐ Apply latest guidelines ⓑ Change in pharmaceutical therapy ⓒ Choice of treatment/management approach ⓓ Change in current practice for referral ⓔ Change in non-pharmaceutical therapy ⓕ Change in differential diagnosis ⓖ Change in diagnostic testing ⓗ Other, please specify: _____

28. How confident are you that you will be able to make your intended changes?

ⓐ Very confident ⓑ Somewhat confident ⓒ Unsure ⓓ Not confident

29. Which of the following do you anticipate will be the primary barrier to implementing these changes?
ⓐ Formulary restrictions
ⓑ Time constraints
ⓒ System constraints
ⓓ Insurance/financial issues
ⓔ Lack of interprofessional team support
ⓕ Treatment related adverse events
ⓖ Patient adherence/compliance
ⓗ Other, please specify:

Please retain a copy for your records. Please print clearly.

First Name
Last Name
E-Mail

The following is your: ☐ Home Address ☐ Business Address

Business Name
Address
City State
ZIP
Telephone # - -
Fax # - -

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

Lesson 117739 RO-OSC-0319

30. Additional comments on this course:

Rate the quality of the material provided:
1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

31. The content was evidence-based. ① ② ③ ④ ⑤

32. The content was balanced and free of bias. ① ② ③ ④ ⑤

33. The presentation was clear and effective. ① ② ③ ④ ⑤

34. Based upon your participation in this activity, do you intend to change your practice behavior? ① ② ③ ④ ⑤

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Twice the Conditions, Twice the Fun

While the presence of other corneal abnormalities makes things difficult for this keratoconus patient, CXL should be initiated as soon as disease progression is detected. **Edited by Joseph P. Shovlin, OD**

Q I have an 18-year-old keratoconus (KC) patient with progressive disease on topography and acuity reduction who appears to be a good candidate for corneal crosslinking (CXL). However, he had a bad adenoviral infection about nine months ago and still has residual subepithelial infiltrates (SEIs) that he is taking topical cyclosporine for. When would it be safe to do CXL, if ever?

A The patient's SEIs may confound a clinician's ability to isolate the underlying cause(s) of acuity reduction and topographic progression, according to Clark Chang, OD, director of cornea specialty lenses at Wills Eye Hospital and director of clinical services at TLC Vision. Further complicating things, Dr. Chang notes that, although ultraviolet (UV) light irradiation has antimicrobial and antifungal therapeutic properties, it is not yet known how UV emissions during CXL affect viral residence within the cornea. These clinical factors make it difficult to determine CXL candidacy and treatment timing for this patient.

Next Steps

Dr. Chang says the conservative management approach would be to provide additional topical therapies to aggressively reduce or eliminate the SEIs prior to CXL treatment.

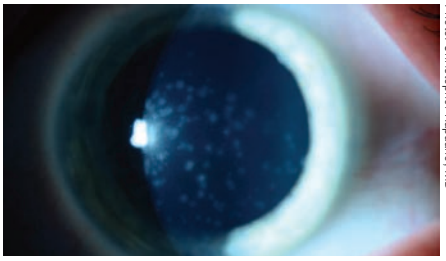


Photo: Christopher Rapuano, MD

This patient has persistent SEIs.

He suggests adding topical corticosteroids to the current topical regimen of cyclosporine and says it may be worth increasing the dosing frequency of either topical medication, or both, in the short term to attempt to obtain quicker clinical control on the inflammatory activities within the cornea.

Progressing with Progression

KC management, however, must maximally protect patients from potentially preventable loss of function. Dr. Chang notes that the decision to provide CXL to a KC patient does not always require documented disease progression. However, given the presence of SEIs that could complicate treatment, he says it is wise to first obtain definitive documentation.

If SEIs are deemed quiescent by the clinician, Dr. Chang says they presumably will not interfere with tomographical tests. Thus, he recommends documenting any corneal changes in posterior corneal elevation profile, posterior corneal curvature and pachymetric distribution.

Due to the patient's young age, Dr. Chang says he'll have a higher risk for KC progression over his lifetime. So, despite the presence of SEIs, if KC progression is detected, even if it is only mild, he notes that providing CXL treatment may be justified given the deterioration in visual function. Before proceeding with CXL under these circumstances, however, Dr. Chang suggests providing education on the off-label use of CXL and the post-op risk of exacerbated SEIs.

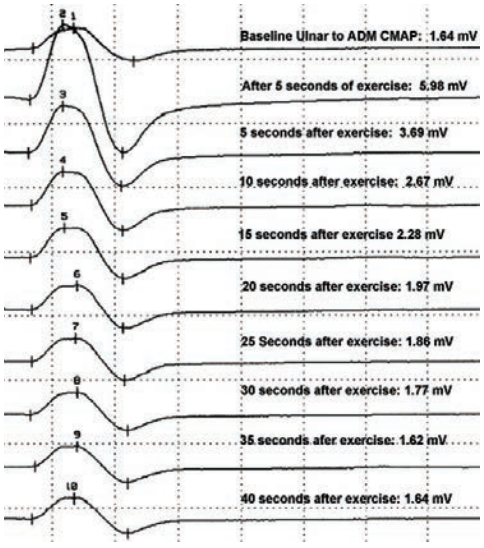
If the patient and his parents have concerns and decide against immediate CXL treatment, Dr. Chang recommends continuing the previously discussed topical therapies and monitoring the cornea every one to two months. This, he adds, will increase the chances of detecting KC progression at a future time point, which would increase the medical necessity of CXL treatment. If CXL is performed, Dr. Chang suggests stressing the importance of avoiding eye rubbing before and after treatment and keeping the patient on a slower post-op topical steroid taper. ■

Beware the Red Herring LEMS

Lambert-Eaton myasthenic syndrome may present similarly to other neurological diseases. **By Michael Trottini, OD, and Michael DelGiodice, OD, and Kaitlyn Kolzow, BS**

A 72-year-old Caucasian female presented as an emergency office visit with complaints of intermittent, horizontal diplopia and ptosis of both eyes that worsened when she was fatigued. She also described increased difficulty standing up when sitting. Additional history taking revealed increased arthritic-like pain, increased fatigue and variable lower limb weakness.

Her medical history was remarkable for hypothyroidism, rheumatoid arthritis, hypercholesterolemia, Sjögren's syndrome and post-herpetic neuralgia. Surgical history included spinal fusion (L3, L4). Her ocular history was remarkable for keratoconjunctivitis sicca, corneal erosion, cataract and vitreomacular traction syndrome in the left eye.



EMG shows initial increment and gradual decline of compound-muscle action potentials following sustained exercise, characteristic of LEMS.

Evaluation

Best-corrected visual acuity was 20/50 OD and 20/60 OS, attributed to bilateral cataracts. Pupils were equal, round and reactive to light. Intraocular pressures were normal. Given the presentation of progressive, fatigable upper lid ptosis, non-comitant abduction deficits, and normal pupils, myasthenia gravis (MG) was the diagnostic concern. We ordered an ice test to evaluate for improvement of the ptosis and diplopia. The ptosis improved bilaterally while the diplopia remained unchanged.

Taking into account her complaints of lower limb weakness, variable ptosis and diplopia, we scheduled an appointment for consultation with a neurologist for electromyography (EMG) to assess the nerve-muscle conduction of her lower limbs and confirm systemic involvement.

EMG revealed an increment of compound muscle potential (CMAP) amplitude of more than 100% on repetitive nerve stimulation, which is not expected in MG but is most consistent with Lambert-Eaton myasthenic syndrome (LEMS). Laboratory testing came back negative for all antibodies related to MG. Subsequently, additional labs were ordered to investigate for positive calcium-channel antibodies associated with LEMS. Because of the presence of positive calcium channel antibodies and CMAP amplitude of more than 100% on repetitive nerve stimulation, a diagnosis of LEMS was made.

Subsequently, the patient was prescribed 100mg of Mestinon (pyridostigmine, Bausch + Lomb). At her two-week follow-up, there was complete resolution of the diplopia and partial improvement of the ptosis bilaterally. She is currently being managed on 100mg of Mestinon.

Discussion

Lambert-Eaton myasthenic syndrome is a rare autoimmune disease affecting possibly as few as 400 people across the United States. It is caused by autoantibodies against voltage-gated calcium channels in the neuromuscular junction seen as a paraneoplastic syndrome in the setting of small cell lung cancer (SCLC), as well as being idiopathic.[1,2,3] LEMS has a clinical triad of proximal muscle weakness, autonomic symptoms and reduced tendon reflexes; it is also associated with small cell lung cancer in approximately 60% of cases.[2]

LEMS patients may present with symptoms that are quite similar to those with MG, given the similarities in pathophysiology.[2] Additionally, patients with either form of LEMS or MG are more likely to have additional concomitant autoimmune diseases, as was observed in our patient.[4,5] LEMS is diagnosed after the assessment of clinical symptoms and signs, antibody testing and

electrophysiological testing.

LEMS patients test positive for voltage-gated calcium channel (VGCC) antibodies 85 to 90% of the time. EMG testing will show low CMAP that depresses even further when tested at low frequencies—LEMS patients show decreased CMAP amplitudes 94 to 98% of the time.[6] Post-exercise stimulation will show increased CMAP more than 100%, which is considered abnormal and is 100% specific for LEMS, with a sensitivity of 84 to 96%.[6]

The diagnosis of LEMS may be delayed because it has a nonspecific pattern of atrophy that may appear similar to other neurological diseases, particularly in those patients with idiopathic LEMS.[3] In some cases, LEMS may be confused with Guillain-Barre syndrome or amyotrophic lateral sclerosis (ALS).[3] The most common mimic of LEMS, however, is MG. Initial presenting symptoms of MG include ptosis and diplopia, where LEMS most often starts with mild upper leg weakness.[3]

As previously mentioned, there are rare cases (5%) of LEMS that present initially with ocular symptoms in contrast to the 90% of cases of myasthenia gravis that present initially with ocular symptoms.[7] LEMS is virtually excluded in patients who present with ocular weakness first, which can ultimately delay proper diagnosis and additional testing to rule out SCLC commonly associated with LEMS.[3,7] Some patients with MG have an initial presentation of limb weakness, but their weakness is typically of the arms (as opposed to the legs in LEMS) and proceeds from head to feet, which is opposite of what is observed in LEMS.[7]

While practitioners see several clinical similarities between myasthenia gravis and LEMS, the two diseases are serologically different. For LEMS patients, 85% to 90% test positive for VGCC autoantibodies, where 50% to 70% of ocular MG patients test positive for anti-acetylcholine receptor antibodies.[8,9] In patients with systemic MG, up to 90% will test positive for the anti-acetylcholine receptor antibodies.[9]

Treatment

While several diseases may mimic LEMS, it is important to obtain a proper diagnosis so that the correct treatment may be initiated. The treatment of choice for LEMS is 3,4-diaminopyridine (amifampridine).[10,11] This drug can improve muscle strength in patients with LEMS and is generally well tolerated with few side effects.[10] It blocks the efflux of potassium ions on the presynaptic nerve to prolong depolarization, keeping the calcium channels open for longer and allowing for increased release of acetylcholine.[10]

Side effects may include digital paresthesias or gastrointestinal symptoms, while some serious side effects included seizures and tachycardia with higher dosages of the drug.[10] Amifampridine blocks VGCCs, which elongates the action potentials at the motor nerve terminals, allowing for increased activity at the neuromuscular junction.[12] In cases where amifampridine is unavailable, pyridostigmine may be used.[3]

Amifampridine, under the name Firdapse (Catalyst), is the first FDA-approved treatment for LEMS in the United States, and our patient was very eager to talk with her neurologist about switching from her pyridostigmine treatment to amifampridine.[13] The reason she was not initially started on Firdapse was due to the limited clinical use by the neurologist.

When managing these patients, it is important to realize that, despite treatment, many patients still exhibit bothersome diplopia and or ptosis. Supportive measures can include temporary prism or occlusion therapy for patients with persistent diplopia and ptosis. Surgery can be considered in patients whose symptoms are stable for a minimum of six months.

While rare, LEMS is still an important differential to keep in mind for patients who experience variable ptosis and diplopia. LEMS is most commonly seen as a paraneoplastic disorder and while it was determined that this patient had idiopathic LEMS, all patients must undergo CT of the lung to discount SCLC. It is for this reason that LEMS should be considered in the differential diagnosis of a patient with variable ptosis, diplopia and proximal muscle weakness. ■

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CMV: Old Foe, New Victims

Immunocompromised patients aren't the only ones at risk from cytomegalovirus.

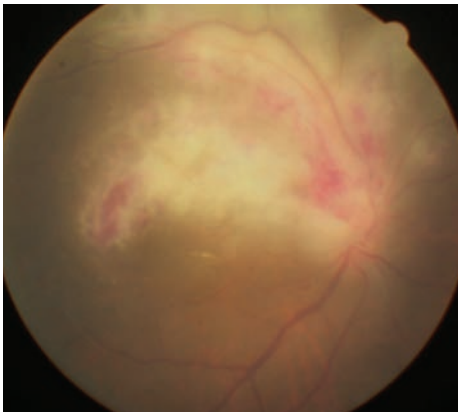
By Carlo Pelino, OD, and Joseph J. Pizzimenti, OD

Viruses are ubiquitous pathogens that can have widespread effects on the body, including virtually all ocular tissues. Some patients are particularly susceptible to certain viruses, such as herpes. Humans are the primary host for eight herpes viruses: herpes simplex 1, herpes simplex 2, varicella-zoster, Epstein-Barr, Human herpesvirus-6, Human herpesvirus-7, Kaposi's sarcoma herpes virus and cytomegalovirus (CMV), which is the cause of several diseases.[1,2] CMV is a large-enveloped, double-stranded member of the *Herpesviridae* family of DNA viruses.

CMV gained recognition during the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) epidemic for causing infectious retinitis in susceptible patients. More recently, it has emerged as a cause of ocular and systemic sequelae in immunocompetent patients.[3,4]

Hostile Takeover

A virus exists as a protein coat, or capsid, that surrounds either DNA or RNA, which codes for the virus elements.[1] A virus cannot reproduce by itself; instead, it inserts its genetic material into the host cell and takes over its functions. In DNA viruses, such as herpes simplex, the viral genetic material is replicated, transcribed (producing mRNA) and translated (creating proteins from the mRNA) when it enters a cell. By this process, the host cell uses the genetic instructions in the virus to make more viruses.[1,2]



This patient diagnosed with AIDS presented with signs of CMV retinitis.

HIV Opens the Door

AIDS, caused by the blood-borne retrovirus HIV, is characterized by profound immunosuppression that leads to opportunistic infections, including CMV. AIDS may also lead to secondary neoplasms, neurological manifestations and death.[1,2] A person's CD4+ T-cell count reliably reflects their current risk of acquiring opportunistic infections.[2]

Approximately 80% of HIV-infected patients will be treated for an HIV-associated eye disorder.[3] Posterior segment findings may include an HIV-associated retinopathy/vasculopathy and a number of opportunistic infections of the retina and choroid.[3]

Infection and Consequences

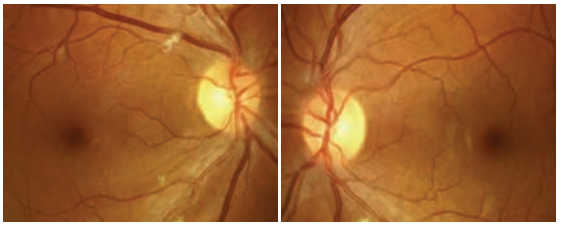
CMV is transmitted from person to person by breast milk, saliva or sexual contact. It can also be transmitted by organ transplantation.[2,3] CMV infects 50% to 85% of adults in the United States by age 40 and is also the virus most frequently transmitted to a child before birth.

Like others in its viral family, CMV has a characteristic ability to remain dormant in the body over a long period. Initial infection, which may have few or even no symptoms, is followed by a prolonged period of infection during which the virus resides in cells without causing detectable damage or clinical illness. Severe impairment of the immune system by medication or disease can reactivate the virus from its dormant or latent state.[1-3]

CMV disease can present with a wide range of manifestations, with colitis being the most common (*Table 1*).[1-4] CMV infection is a particular concern for certain patient populations because of the risk of infection to unborn babies, people who work with children and immunodeficient individuals, such as transplant recipients, cancer patients undergoing chemotherapy and those living with HIV.

CMV retinitis occurs in patients who have failed to generate a primary T-cell response against the virus or who are carriers of CMV but whose previously effective CMV-specific T-cell response has decreased due to disease or immunosuppressive treatment.[3]

CMV produces a characteristic ophthalmoscopic appearance of a pale, necrotic retina, often with focal areas of hemorrhage in a sectoral distribution spreading along vascular arcades. When retinitis is inactive



HIV retinopathy may present with cotton-wool spots, hemes and other vascular changes.

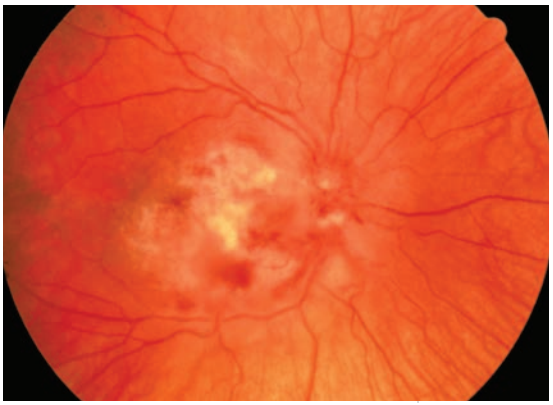


Photo: National Eye Institute, National Institutes of Health

This patient has CMV retinitis with optic disc edema.

following anti-CMV treatment, the retina remains thin and atrophic with clumping of the pigment epithelium.[3] Visual function loss is mainly due to direct extension of the retinitis to the macula or optic nerve head, or retinal detachment.

The diagnosis of CMV retinitis can be confirmed by polymerase chain reaction amplification of viral DNA in the aqueous.[2,3]

Treatment Options

Intravenous administration of the antiviral drugs ganciclovir and foscarnet has modest penetration into the vitreous compared with direct intravitreal injection.[3] In randomized trials of HIV-associated CMV retinitis, a ganciclovir implant was consistently superior to intravenous ganciclovir in preventing progression.[3,4]

Combination anti-HIV treatment effectively controls HIV replication and restores the number and function of CD4+ T-cells, giving most patients a near normal life expectancy. In countries where effective treatment is available, the incidence of HIV-associated CMV retinitis has decreased substantially. It should be noted that in up to 40% of HIV-infected patients with CMV retinitis, initiation of anti-HIV treatment leads to an immune recovery uveitis, which may include anterior uveitis, cataract, posterior uveitis, cystoid macular edema, optic disc edema and epiretinal membrane formation. Treatment with corticosteroids is often necessary in these cases.[3,4]

CMV in the Immunocompetent

Unfortunately, the incidence of CMV disease in immunocompetent adults appears to be greater than previously thought, possibly due to immune dysfunction related to comorbidities, such as diabetes or kidney disease. CMV infection in healthy adults is usually asymptomatic or causes a mild mononucleosis-like syndrome. However, over 380 published case reports document instances of severe, tissue-invasive CMV infection in immunocompetent adults.[4]

Similar to CMV disease in immunocompromised patients, these cases show a wide range of manifestations, including colitis, vascular thrombosis, pneumonia and myocarditis.[3,4] CMV has emerged as a cause of kerato-uveitis, anterior uveitis and retinitis in immunocompetent patients, the complications of which are associated with significant morbidity.[5,6] Along with the common ophthalmic therapies, targeted antiviral therapy with ganciclovir or valganciclovir is appropriate for severe CMV ocular disease in immunocompetent adults.[4,5]

CMV can present with a wide range of ophthalmic manifestations and causes significant morbidity and mortality in neonates and severely immunocompromised adults. However, CMV disease in immunocompetent adults also has been increasingly reported in recent literature, and optometrists should add it to the list of suspected causes of kerato-uveitis, anterior uveitis and retinitis in healthy patients. ■

Table 1. Common CMV Manifestations[1-4]

System	Condition
Gastrointestinal	• Colitis • Enteritis • Gastritis • Hepatitis • Pancreatitis
Respiratory	• Pneumonitis
Hematological/ Cardiovascular	• Thrombocytopenia • Anemia • Myocarditis • Venous thrombosis
Neurological	• Meningitis • Encephalitis • Myelitis • Retinitis • Uveitis

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A Diagnosis for the Birds

You'll need more than a wing and a prayer to explain this patient's complaints.

By Ellen Butts, OD and Mark T. Dunbar, OD

A 61-year-old Caucasian female presented with symptoms of blurred vision in both eyes for the past year and a half. She also reported seeing dark floaters in her vision that she described as having white halos surrounding them.

Her past ocular history was significant for a retinal detachment in the left eye four years earlier that was repaired with a gas bubble and laser. She then developed an epiretinal membrane in the same eye, which was treated with a vitrectomy, and then cataracts in both eyes, which resulted in cataract surgery two years prior. She felt her vision was good after the cataract surgery but now reported a painless progressive decline in her vision in both eyes with floaters. Her past medical history was unremarkable.

On examination, her best-corrected visual acuity was 20/40 OD and 20/60 OS. Confrontation visual fields were full to careful finger counting OU, and the pupils were equally round and reactive with no afferent pupillary defect. The anterior segment was significant for trace cell in the anterior chamber of the right eye and 1+ cell in the left eye with trace flare. A posterior chamber intraocular lens (IOL) was present in both eyes with 2+ capsular opacification in the right eye.

Dilated fundus exam showed a significant vitritis in both eyes. The optic nerves appeared healthy with small cups and good rim coloration and perfusion in both eyes.

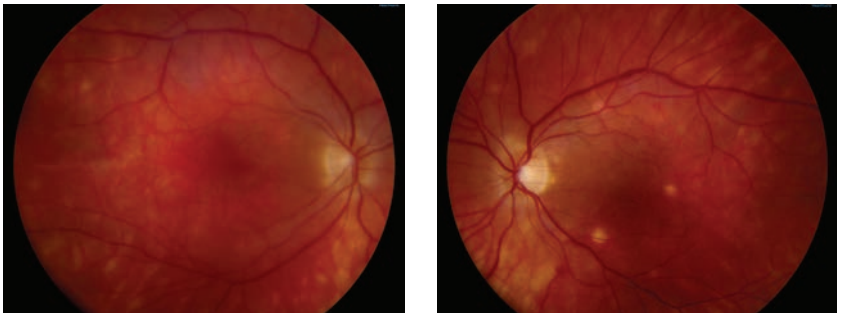


Fig. 1. These fundus shots show noticeable changes to the patient's retina.

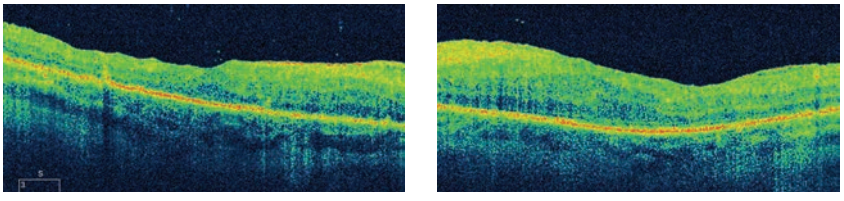


Fig. 2. These OCT images illuminate specific findings along the layers of the posterior segment, including the choroid.

The arteries and veins were slightly attenuated. There was an absence of the fovea light reflex in both macules. Throughout the posterior pole and peripheral retina, there were obvious retinal changes (*Figure 1*). An optical coherence tomography (OCT) image was ordered as well (*Figure 2*).

Take the Retina Quiz

1. What additional tests would be helpful to confirm the diagnosis?
a. Fluorescein angiography.
b. HLA-A29.
c. Angiotensin-converting enzyme.
d. HLA-B9.

2. What does the OCT show?
a. Neurosensory retinal detachment.
b. Cystoid macular edema.
c. Mild inner retinal thickening but no cystoid macular edema.
d. Loss of the IS/OS junction.

3. What is the likely diagnosis?
a. Multifocal choroiditis and panuveitis.
b. Serpiginous choroiditis.
c. Birdshot chorioretinopathy.
d. Syphilis.

4. What is the best treatment?
a. Corticosteroids.
b. Observation.
c. Immunosuppressive agents.
d. Both a and c.

Discussion

Based on the history and the clinical presentation of multiple creamy-white fundus lesions at the level of

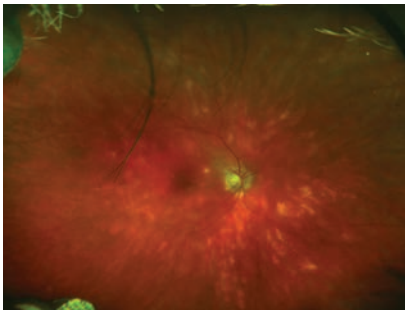
the choroid, with vitreous inflammation, we were very suspicious that our patient had "birdshot chorioretinopathy," a rare autoimmune inflammatory condition of the choroid and retina. Blood work was performed, including HLA-A29, which came back positive, thus confirming our initial suspicion of birdshot.

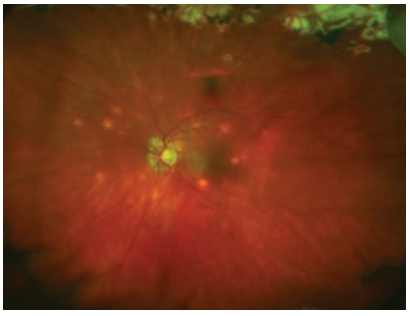
Birdshot retinochoroidopathy (BSCR) occurs in men and women in the fifth to seventh decade of life, mostly in Caucasian patients.[2-3] The most common symptoms are blurred vision, increasing floaters and photopsia.[2] As the disease progresses, night blindness and loss of color vision can occur.[2] Our patient did have reduced color vision in both eyes; only seeing 6/11 Ishihara color plates in the right eye and 3/11 in the left eye.

The hallmark of the disease is significant vitritis and multifocal patches of depigmented or hypopigmented lesions that may be creamy yellow or orange in color. The ill-defined patches are typically round or oval in shape. Some will be elongated in a pattern that radiates toward the peripheral fundus. The striking feature of the lesions is the lack of chorioretinal scaring or hyperpigmentation at the margins that is often seen in other inflammatory conditions. The origin of the disease begins in choroid and later involves the retinal pigment epithelium.

The diagnosis is usually made based on clinical presentation; however, it is also strongly associated with the HLA-A29 antigen.[2-3]

Researchers hypothesize that enhanced expression of self-peptides to T-lymphocytes through the A29 molecule or through molecular mimicry with microbial antigen is a key driver in the disease.[3] Given this strong association with the HLA-A29 antigen, many believe that "HLA-A29 uveitis" is a more appropriate name for BSCR.[3]





These fundus images show the patient four years following her initial diagnosis.

Fundus autofluorescence (FAF) can help diagnose BSCR as well as the long-term follow up. The most common FAF finding is peripapillary confluent hypoautofluorescence and abnormal macular FAF. Peripapillary hypoautofluorescence is strongly related with age and disease duration. Global hypoautofluorescence (i.e., present in both the macula and extramacular region) suggests that hypoautofluorescence may be a marker for chronicity and severity of BSCR.[4]

BSCR is a chronic, slowly progressive condition that has bouts of remissions and exacerbations.[2] Vision loss often occurs due the development of cystoid macular edema, which develops from chronic inflammation.[2] The emphasis for treatment is to quiet the inflammation. Corticosteroids have been the mainstay in treatment with limited success. Immunosuppressive agents such as methotrexate, mycophenolate mofetil and cyclosporine have also been used alone or in combination when corticosteroids for long term treatment.[2] Cellcept (mycophenolate, Genentech) is thought to induce apoptosis of the lymphocytes as well as inhibiting recruitment of lymphocytes.

Our patient was treated with topical prednisolone acetate 1% and topical diclofenac 0.1% both QID, as well as oral corticosteroids and mycophenolate 1gm PO bid. The vitreous floaters improved but over the course of a few months she subsequently went on to develop CME in both eyes, which was treated with dexamethasone intravitreal implants (Ozurdex, Allergan). This helped to control the inflammation and improve her CME for several months, but her course continued to wax and wane. She ultimately had a Retisert (Bausch + Lomb) implant in both eyes, which resulted in resolution of her CME. Retisert is a 0.59mg fluocinolone acetonide time-release, sterile implant designed to deliver corticosteroid therapy to the posterior segment for approximately two and a half years.[5] She continues to be closely followed; however, she also had developed elevated IOP due to the chronic steroid use, which is being treated with IOP lowering medications. ■

Dr. Butts is an optometry resident at Bascom Palmer Eye Institute.

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A Stroke of Bad Luck

By the time you see this, it may be too late to save vision, but your responsibility doesn't end there. **By Jim Williamson, OD, Theresa Cassidy, OD, and Richard Mangan, OD**

Sudden-onset, unilateral, painless vision loss is certainly a cause for patient and doctor concern as it may indicate acute retinal ischemia (ARI). Transient monocular vision loss (TMVL) is the most common symptom of ARI with an incidence of approximately 14 per 100,000.[1] Ophthalmic exams on TMVL patients usually lack significant findings and sequelae. In contrast, ARI from artery occlusions produce permanent visual acuity, visual field loss, or both.[1] Though treatment is mostly futile in restoring vision in these cases, patients should still be emergently referred for a stroke work-up.[2]

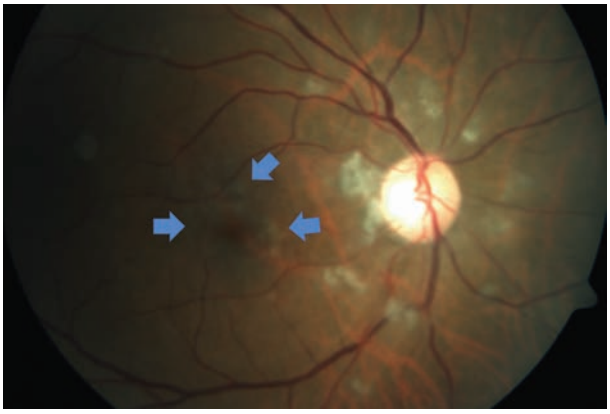

Fig. 1. This right eye fundus photograph documents the presence of cotton-wool spots surrounding the optic nerve. More subtle signs of ischemia surround the fovea (arrows). Vessel caliber appeared mostly symmetrical with the unaffected eye.

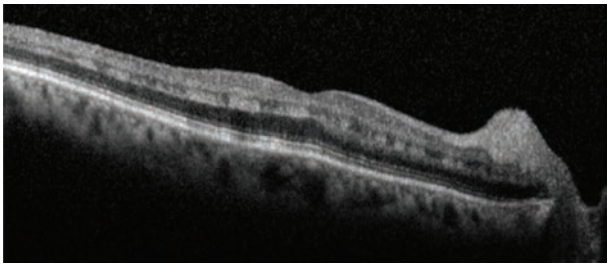

Fig. 2. Hyperreflective bands in the inner nuclear layer consistent with paracentral acute middle maculopathy.

The Patient

A 77-year-old African-American male presented with a complaint of constant black spots in his right eye for one week that did not change with eye movement. He also reported reduced vision in the right eye along with weakness on the right side since its onset. His best-corrected visual acuity was 20/20-2 OD with +0.75DS, and 20/20 OS with +0.25-0.50x105.

Pupils were equally round and reactive and without an afferent pupillary defect (APD). Both extraocular motilities and confrontation visual fields were unremarkable. Amsler grid was unreliable in the right eye due to problems fixating centrally. His medical history included anemia, hypertension and hyperlipidemia. His ocular history was positive for uncomplicated cataract surgery with posterior chamber intraocular lenses (PC-IOL) OU in 2014. His medications included allopurinol, hydrochlorothiazide, levetiracetam, potassium chloride and sildenafil.

Anterior segment examination showed a clear PC-IOL OD and a PC-IOL OS with temporal posterior capsular opacification in the left eye. Intraocular pressures were 10mm Hg OD and 11mm Hg OS with Goldmann applanation tonometry. A dilated fundus exam revealed 0.3 round cup-to-disc ratios with distinct margins in both eyes, paramacular retinal whitening in the right eye and cotton-wool spots surrounding the right nerve *(Figure 1)*. The left eye was unremarkable. Same-day ancillary testing included optical coherence tomography (OCT-B) with angiography (OCT-A), and intravenous fluorescein angiography. A visual field was not performed due to the urgency from the above test results.

OCT-B detailed hyperreflective bands at the level of the inner nuclear layer consistent with paracentral acute middle maculopathy (PAMM) *(Figure 2)*. OCT-A highlighted intereye asymmetrical superficial vessel density and choriocapillaris blood flow *(Figures 3 and 4)*. The IVFA recorded an extended arm-to-retina time of 45 seconds with a significant delay of subsequent phases in the right eye (*Figure 5*). Auscultation of the right carotid was negative for a bruit.

The patient was referred to the emergency room with the eye care providers alerting doctors prior to

his arrival. A magnetic resonance imaging scan was negative for any acute intracranial abnormalities. A computed tomography angiogram detected a stenosed right ophthalmic artery without significant carotid artery occlusion *(Figure 6)*.

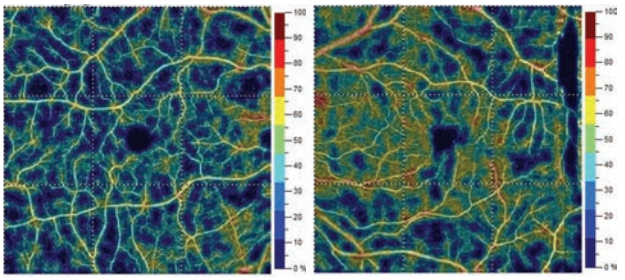

Fig. 3. Color map representation of superficial vessel density percentages OD (left) versus OS (right). Comparative grid-based vessel density between the eyes varied from 2% to 15%.

Follow Up

ARI events are classic causes for sudden monocular vision loss and usually result from an embolic episode.[1,2] From a vascular standpoint, unilateral visual disturbances often trace to the anterior cerebral circulation (i.e., the internal carotid artery, or ICA). Of significance to the optometrist is the first branch of the ICA—the ophthalmic artery—which subsequently divides to provide circulation to the optic nerve, choroid and retina.[3]

An occluded ophthalmic artery (OAO) produces profound ischemia and vision loss (light perception or no light perception) as both the retina and choroid are left devoid of circulation. This patient's visual acuity (20/20-2) and pupil findings (no APD) are attributed to the partial vs. full OAO. In this case, hemodynamic disturbances unrelated to an embolus resulted in ocular ischemia. Hayreh explained this through his anatomical studies, which discussed perfusion pressure. He demonstrated that a stenosed ophthalmic artery with little or no ICA stenosis is primarily responsible for the fall in blood pressure in the ocular vascular bed.[4]

Clinically, a complete OAO lacks the "cherry red spot" seen in central retinal artery occlusions due to the lack of choroidal blood flow. Retinal vessel constriction and optic disc edema are also seen. Later in the disease, retinal pigment epithelium (RPE) alterations occur.[5] The Almaric sign, which appears as triangular patches of retinal whitening during posterior choroidal artery occlusion, may be present.[6] These patches mostly point toward the posterior pole or disc and result from infarction deep within the retina, which causes outer nuclear layer and RPE necrosis.[6]

The presence of hyperreflective bands seen on OCT-B in this patient is characteristic for PAMM, which affects the middle layers of the macula and indicates ischemia.[7] These bands co-localize precisely with the intermediate and deep vascular plexi, which in tandem comprise the deep vascular plexus.[8]

Besides stenotic and embolic etiologies, OAO can also be due to hypercoagulable states or a vasculitis such as giant cell arteritis. Appropriate bloodwork should be ordered for these entities. Several authors report OAO following injection of cosmetic facial fillers such as autologous fat or hyaluronic acid.[6,9] Optometrists should be aware of this given the rising popularity of these procedures. Others cite illicit drug use as an origin for OAO. Cocaine produces prolonged vasoconstriction and enhances platelet aggregation, while intravenous drugs often contain the filler talc, which can be potentially embolic.[10]

A lesser discussed condition called "Saturday night retinopathy" should also be considered with OAO. In this instance, OAO occurs with an acute rise in orbital cavity pressure by direct compression of the orbit when a patient falls asleep in a stuporous state following heavy alcohol or drug use.[11]

Though proposed treatments fail at restoring vision in patients with ARI secondary to an arterial occlusion, both the National Stroke Association and the American Heart Association consider "retinal cell death attribut-

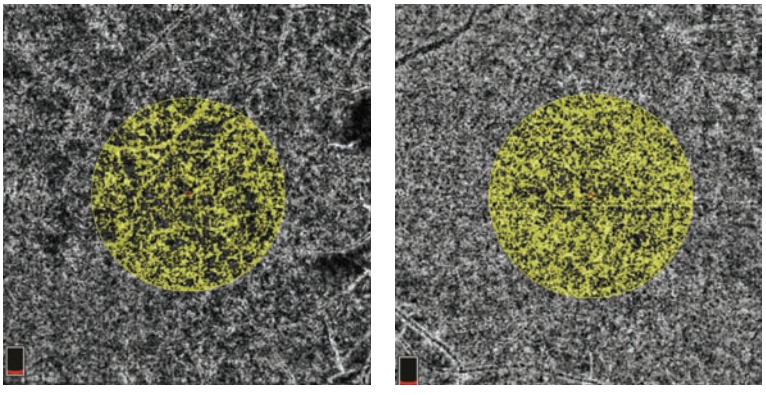

Fig. 4. In this OCT-A image, the right eye (left) shows a choriocapillaris flow area of 3.763mm² surrounding the fovea in an examiner-selected area of 7.114mm². The left eye has an increased flow area of 4.686mm² within the same area.

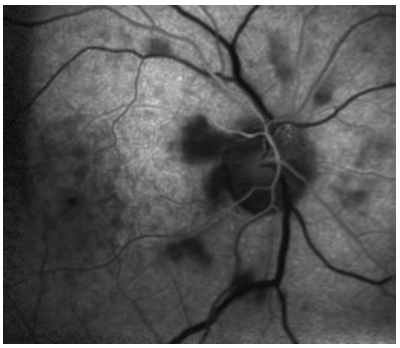

Fig. 5. The depicted arterial phase of the fluorescein angiography occurred at three times that of a normal eye, which indicates delayed blood flow.

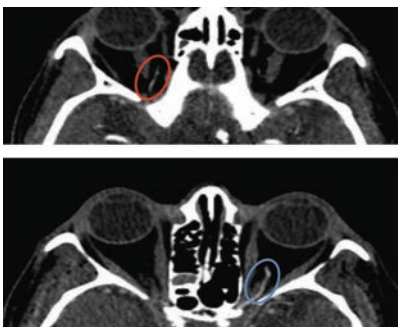

Fig. 6. CT angiogram reveals a stenotic right ophthalmic artery (top, red oval) compared to the unaffected left ophthalmic artery (bottom, blue oval).

able to ischemia" as a stroke equivalent.[2] Recognizing an arterial occlusion as the cause for an ARI puts optometrists at the interventional front in these cases. This is significant, considering stroke is the fifth most common cause of death in the United States.[12] Low vision services should also be discussed with patients who suffer visual loss that interferes with their activities of daily living. ■

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Diagnostic **Quiz**

The Skinny on Peculiar Skin

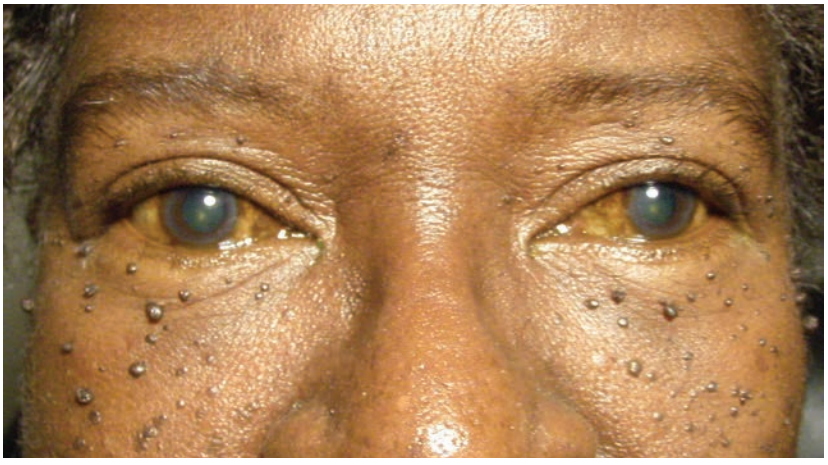
By Andrew S. Gurwood, OD

History

A 67-year-old black female reported to the office with a chief complaint of blurry vision at near, as well as facial skin lesions. She asked if there was any medication that could improve her skin cosmesis. Her systemic history was remarkable for hypetension, diabetes and dyslipidemia, which was well controlled medically with lisinopril, metformin and a statin, respectively.

Diagnostic Data

Her best-corrected entering visual acuities were 20/20 OD and OS at distance and 20/30 at near. Her near acuity was improved by increasing her add power and ensuring she was holding the print within the correct focal region of her progressive addition lenses. Her external examination was normal. The skin condition is illustrated in the photograph. The biomicroscopic examination of the anterior segment was normal with Goldmann applanation tonometry measured at 15mm Hg OU. The dilated fundus examination of the posterior pole revealed optic nerves with cup-to-disc ratios measuring 0.3/0.3 and no peripheral pathologies OU.



This 67-year-old woman is suffering from both skin lesions and blurry vision. Can you identify the cause of her visual disturbances?

Your Diagnosis

Does this case require any additional tests? What steps would you take to manage this patient? Based on the information provided, what would be your diagnosis? To find out, please visit www.reviewofoptometry.com. ■

Retina Quiz Answers *(from page 102):* 1) b; 2) c; 3) c; 4) d.

Next Month in the Mag

Coming in April, *Review of Optometry* will present its Annual Cornea Report.

Topics include:

- *My Patient Has Recurrent Corneal Erosion—Now What?*
- *Systemic Conditions that Affect the Cornea*
- *2019 Update on Keratoconus*
- *How You Can Remove Foreign Bodies* (Earn 2 CE Credits)

Also in this issue:

- *Extended Depth of Focus Lenses: How Do They Work?*
- *A Guide to Special Interest Groups in Optometry*

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