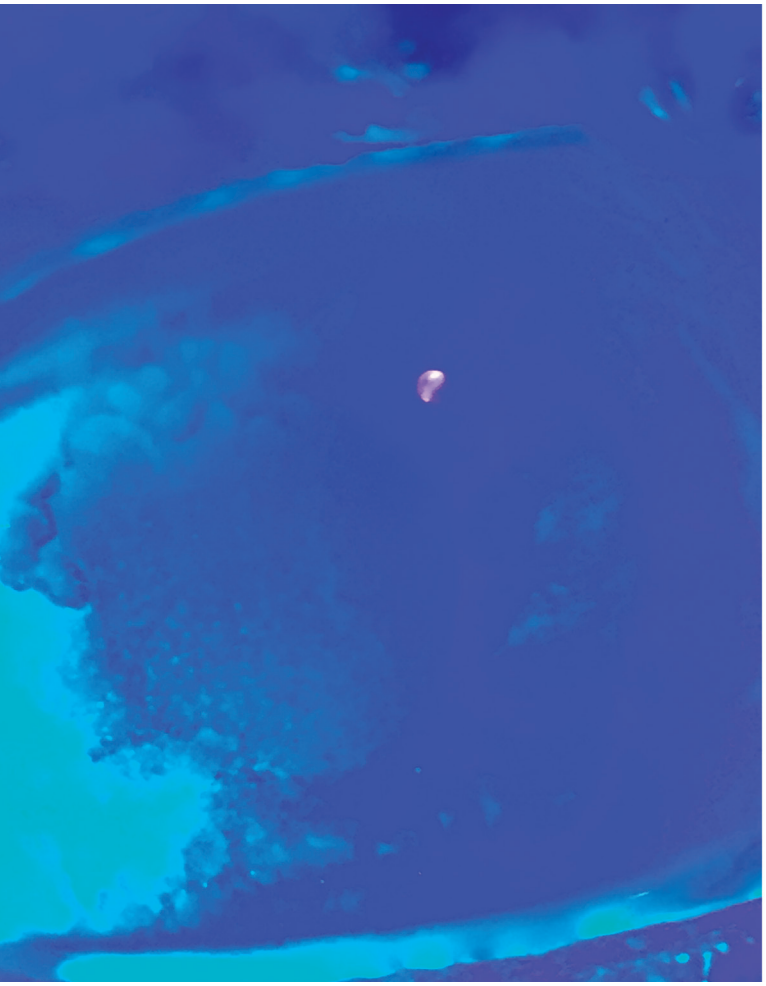
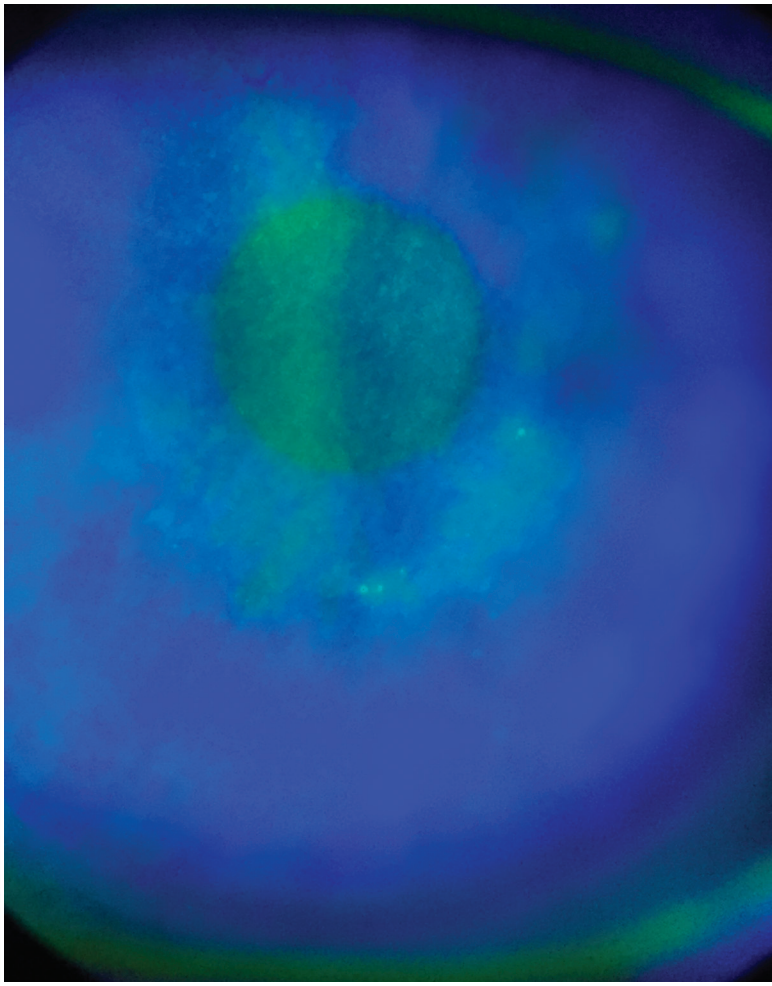
Ophthalmology MANAGEMENT
Glaucoma PHYSICIAN

DECEMBER 2020

The Crossroads of Glaucoma and Ocular Surface Disease

BUILDING A TREATMENT PLAN FOR REAL CLINICAL SUCCESS





HIGHLIGHTS FROM A WEBINAR FEATURING:
Preeya Gupta, MD • Nathan Radcliffe, MD

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. U.S. Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1. Accessed April 17, 2020. **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [prescribing information].East Hanover, NJ: Novartis Pharmaceuticals Corp; November 2019.

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

5/20 XIA-1388813

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

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

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

In five clinical studies of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation Day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation Day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing five, 400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation Days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

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

Manufactured for:
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

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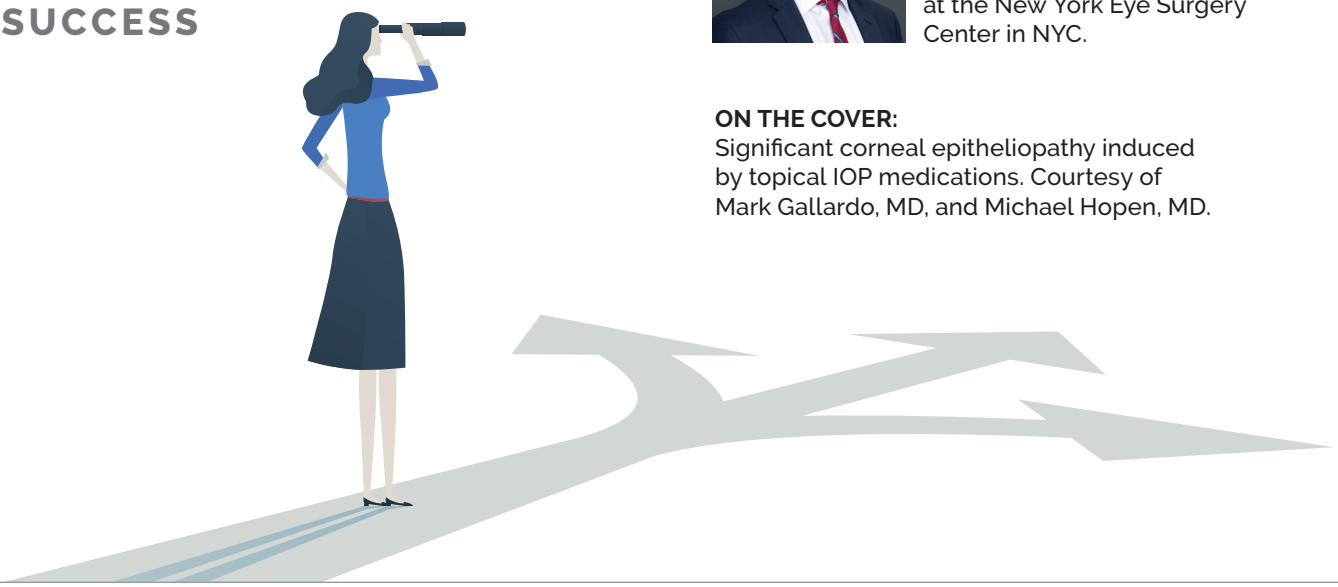
The Crossroads Of Glaucoma And Ocular Surface Disease

BUILDING A TREATMENT PLAN FOR REAL CLINICAL SUCCESS



FACULTY

Preeya K. Gupta, MD
Dr. Gupta is an associate professor of ophthalmology, cornea & refractive surgery, and clinical director of Duke Eye Center at Duke University in Durham, NC.

Nathan Radcliffe, MD
Dr. Radcliffe is an associate professor of ophthalmology, Mount Sinai School of Medicine in New York City, and is surgeon at the New York Eye Surgery Center in NYC.

ON THE COVER:
Significant corneal epitheliopathy induced by topical IOP medications. Courtesy of Mark Gallardo, MD, and Michael Hopen, MD.

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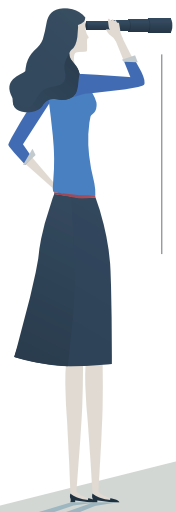
The Crossroads of Glaucoma and Ocular Surface Disease

BUILDING A TREATMENT PLAN FOR REAL CLINICAL SUCCESS

The genesis of this program was the realization that glaucoma patients with dry eye disease are really suffering, and with the steady flow of innovative new therapies for glaucoma and for ocular surface disease (OSD) that are being introduced regularly, ophthalmologists are equipped with many opportunities to better protect patients' vision and also help to alleviate their discomfort.

This discussion between **Nathan Radcliffe, MD,** and **Preeya Gupta, MD,** highlights some of the latest therapeutic advances in glaucoma and OSD. Here, they present real-world cases that illustrate how to integrate these treatments within a patient's care plan for optimal results.



CASE 1: NEWLY DIAGNOSED POAG WITH MGD

Dr. Radcliffe: This 65-year-old woman was newly diagnosed with primary open-angle glaucoma (POAG). Her best corrected visual acuity is 20/20; IOPs are 24 mmHg in the right eye and 23 mmHg in the left eye. Corneal thickness is normal (550 microns) in both eyes, and visual fields are full.

Cirrus HD-OCT (Carl Zeiss Meditec) shows retinal nerve fiber layer (RNFL) loss inferiorly in both eyes, extending into the maculas. A PanoMap analysis, which is a widefield structural damage assessment, confirms inferior RNFL defects extending into the macula in both eyes. This is early glaucoma.

Upon clinical examination, I identified meibomian gland dysfunction (MGD), which for this patient is asymptomatic, and mild conjunctival hyperemia (Figure 1). Mild expression produced some inspissated secretions.

Historically, our first-line therapy for patients with early glaucoma is a topical antiglaucoma medication. Prostaglandin analogue (PGA) monotherapy is considered the initial treatment of choice, although selective laser trabeculoplasty (SLT) is becoming a popular option.[1]

PGAs are currently our first choice among the topical medications because they have excellent 24-hour efficacy, QD dosing, and a favorable systemic safety profile. Latanoprost is widely available as

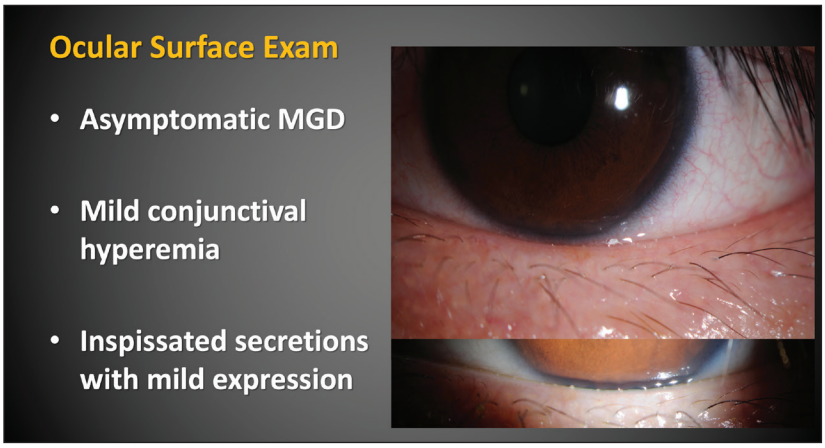


Figure 1. Clinical exam of a patient newly diagnosed with POAG revealed MGD and mild conjunctival hyperemia.

a generic formulation, but we do have some other agents that, in all likelihood, are more efficacious than latanoprost. They include:

- **Bimatoprost** (Lumigan, Allergan). Studies have shown a switch from latanoprost to bimatoprost reduces IOPs in latanoprost nonresponders.[2]
- **Latanoprostene bunod** (Vyzulta, Bausch + Lomb). This medication has been shown to be more efficacious than latanoprost by 1.24 mmHg.[3]
- **Netarsudil/latanoprost** (Rocklatan, Aerie Pharmaceuticals). This once-daily, fixed-combination medication has been shown to be more efficacious than latanoprost by an additional 1.3 mmHg to 2.5 mmHg.[4]

With several topical options from which to choose, it behooves us to prescribe the most efficacious agent to decrease the chance a patient will need more than one medication.

Dr. Gupta, should I immediately choose pharmacotherapy for this patient with glaucoma and MGD?

Dr. Gupta: Traditionally, that has been our approach, and it's certainly not wrong to start a PGA, but I think we should be more proactive in thinking about what that topical drop will do to the ocular surface. If you were to ask any number of cornea specialists if antiglaucoma medications cause issues on the ocular surface, I believe everyone would say yes, unequivocally. These drops can cause allergies, and many patients are intolerant. Hyperemia is also an issue, particularly with certain classes of medications, and many of these medications contain benzalkonium chloride (BAK), a preservative that is pro-inflammatory and toxic to the ocular surface.[5]

This patient is treatment-naïve, and she may require therapy for 30 or more years of her life, even if it is just a single-agent eye drop. We know glaucoma doesn't behave how we want it to, so she may require multiple therapies throughout the years; and OSD has visual function related implications, especially for patients with glaucoma, so we want to include the ocular surface in our treatment decision making.

When I talk to these patients, they say their number-one concern is that they can't see well, and glaucoma is a blinding disease. But here's the paradox: We're trying to save patients from this blinding disease, but in doing so, we may be compromising their visual function and their overall happiness with their vision.

I urge all of my glaucoma colleagues to examine the ocular surface and use that as one parameter in their decision-making process, because when we consider the lifetime of someone with glaucoma and someone on therapy, we're making a critical decision.

We know from the literature that there is a high prevalence of OSD in patients with glaucoma. Zhang and colleagues reported that more than 50% of patients using antiglaucoma medications have OSD.[6] What's more, many of our glaucoma patients are older and have MGD or are using systemic medications that can exacerbate the situation.

The prevalence and severity of OSD symptoms correlate with how often patients use a drop and with the chronicity of BAK exposure.

Leung and colleagues found a twofold increase in the likelihood of developing OSD with each additional BAK-containing drop prescribed.[7] When we adhere to our traditional treatment paradigms, we prescribe a topical medication, and if it doesn't work, we add another topical medication. This can spiral quickly into a situation where patients are not happy.

Not all medications are the same in how they interact with the ocular surface. PGAs are likely to induce hyperemia, and they also cause MGD and meibomian gland atrophy over time.[8] Alpha-adrenergic agonists have a high ocular allergy rate.[8] Carbonic anhydrase inhibitors can increase corneal thickness.[8] Interestingly, there is a beta receptor on the lacrimal gland, and a beta-blocker can reduce the basal tear turnover rate and alter mucus production.[8]

According to several studies, PGAs are highly associated with MGD. Mocan and colleagues found that 92% of patients using a PGA compared with 58% using a non-PGA medication had some signs of MGD.[9] Arita and colleagues showed a higher prevalence of meibomian gland atrophy after long-term use of topical antiglaucoma medications.[10] I believe there are parallels between meibomian gland atrophy and RNFL damage.

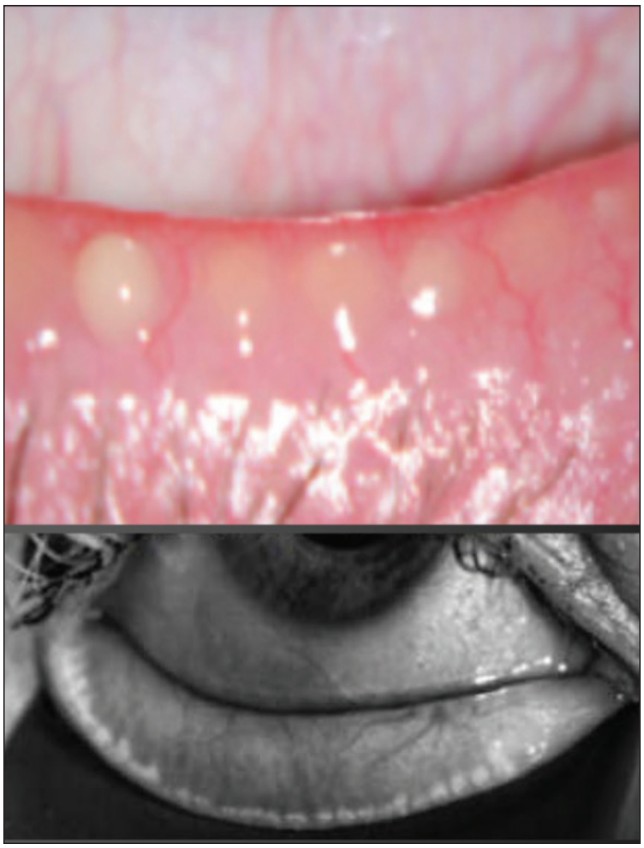


Figure 2. Long-term use of some topical antiglaucoma medications permanently damages the meibomian glands.

We may not pay as much attention to the meibomian glands, because they're not causing blindness in the way that losing fibers in the optic nerve causes blindness. However, severe meibomian gland atrophy (Figure 2) is irreversible. I take this very seriously, and in the thick of our day, when we're worrying about patients losing nerve fibers in their optic nerve or their meibomian glands, we need to pay attention to both because both are irreversible processes.

Key considerations for this patient include:

1. Antiglaucoma medications lead to ocular surface compromise, which increases with the length of exposure and the number of agents used.
2. In treatment-naïve patients, an OSD clinical examination will help determine the risk of worsening dry eye disease or MGD when choosing treatment options. If a patient is asymptomatic today, we need to look at his or her risk factors, and the signs of OSD should be assessed as risk factors.
3. Consider non-topical pharmacologic therapy, such as SLT, as first-line or early treatment for patients who have elevated IOPs and are at risk for OSD.

SLT AS A FIRST-LINE OPTION

Dr. Radcliffe: We have ample evidence supporting the use of SLT as primary and secondary therapy to treat glaucoma.[11,12] Although the efficacy of SLT is similar to that of latanoprost, we probably don't use it as often as we should, and we underappreciate its benefits to practice, patients, and payers.[13,14] Data from the LiGHT study are changing this mindset.

The LiGHT study is a randomized, controlled trial in which 718 treatment-naïve patients were treated with either SLT or topical antiglaucoma therapy.[15] At 36 months, about 75% of patients in the SLT group maintained target IOPs without topical medications.

> We're trying to save patients from this blinding disease, but in doing so, we may be compromising their visual function and their overall happiness with their vision.
>
> **—Preeya Gupta, MD**

Eyes in the SLT group were within target IOP at more visits than those in the topical medication group. The rate of disease deterioration, as determined by visual fields, was 3.8% in the SLT group compared with 5.8% in the topical medication group. In addition, more of the patients using topical medications needed treatment escalation (348) compared with those in the SLT group (299). As for glaucoma surgeries, 11 patients in the medication group needed surgery compared with zero in the SLT group.

This study concludes that SLT is a valid first-line therapy for ocular hypertension and glaucoma and is associated with better overall outcomes than topical medications. To me, this signals a change in the standard of care.

OUTCOME

Dr. Radcliffe: I treated this patient with SLT in both eyes (I use the Duet laser platform [Lumenis], which is a combination YAG and SLT laser). Six weeks later, her IOPs were 16 mmHg and 17 mmHg, which is an excellent pressure reduction, similar to what was seen in the LiGHT study.

The patient continues to be asymptomatic with MGD. She had no new complaints, which we might have seen if we had used topical medications. From this case, we can conclude that SLT is an ideal primary therapy for patients with glaucoma and MGD.

CASE 2: LONG-STANDING POAG, WORSENING DRY EYE

Dr. Gupta: This 67-year-old woman reported worsening dry eye symptoms, including foreign body sensation, blurred vision, and redness. She has a history of dry eye and POAG for more than a decade. She uses artificial tears liberally, warm compresses, and ointment at night. She recently stopped using latanoprost because she believed it was irritating her eyes, and she couldn't tolerate it. She underwent successful SLT in 2008 and had a second SLT treatment in 2017.

The patient has significant corneal staining, fine telangiectasia, and 2+ MGD in both eyes. Her tear breakup time (TBUT) is 4 seconds, and MMP-9 testing indicates elevated levels of this inflammatory marker in both eyes. The patient's IOPs are not well-controlled and have increased to untreated baseline: 24 mmHg for the right eye and 27 mmHg for the left eye. Best corrected visual acuity is 20/30 OU. Meibomian gland imaging shows some mild atrophy in the right eye and moderate atrophy in the left.

I incorporate meibomian gland imaging into my clinical examination because it tells me what has been happening over time, since we know the meibomian glands don't die off instantaneously. It's also a great educational tool that I use to show patients visually what's happening on the ocular surface. It makes me a better clinician and helps me stage the severity of a patient's MGD.

Dr. Radcliffe: The PanoMap analysis of the optic nerve and macula of the left eye shows diffused thinning of the RNFL and some inferotemporal bundle defects. (I'm expecting to see a superior change in the visual field.) The vertical cup-to-disc ratio is still only about 0.55. The deviation map shows an arcuate scotoma and inferior damage.

The key considerations for this patient include:

1. Poorly controlled IOPs with glaucomatous optic nerve damage
2. Intolerance of topical antiglaucoma medications

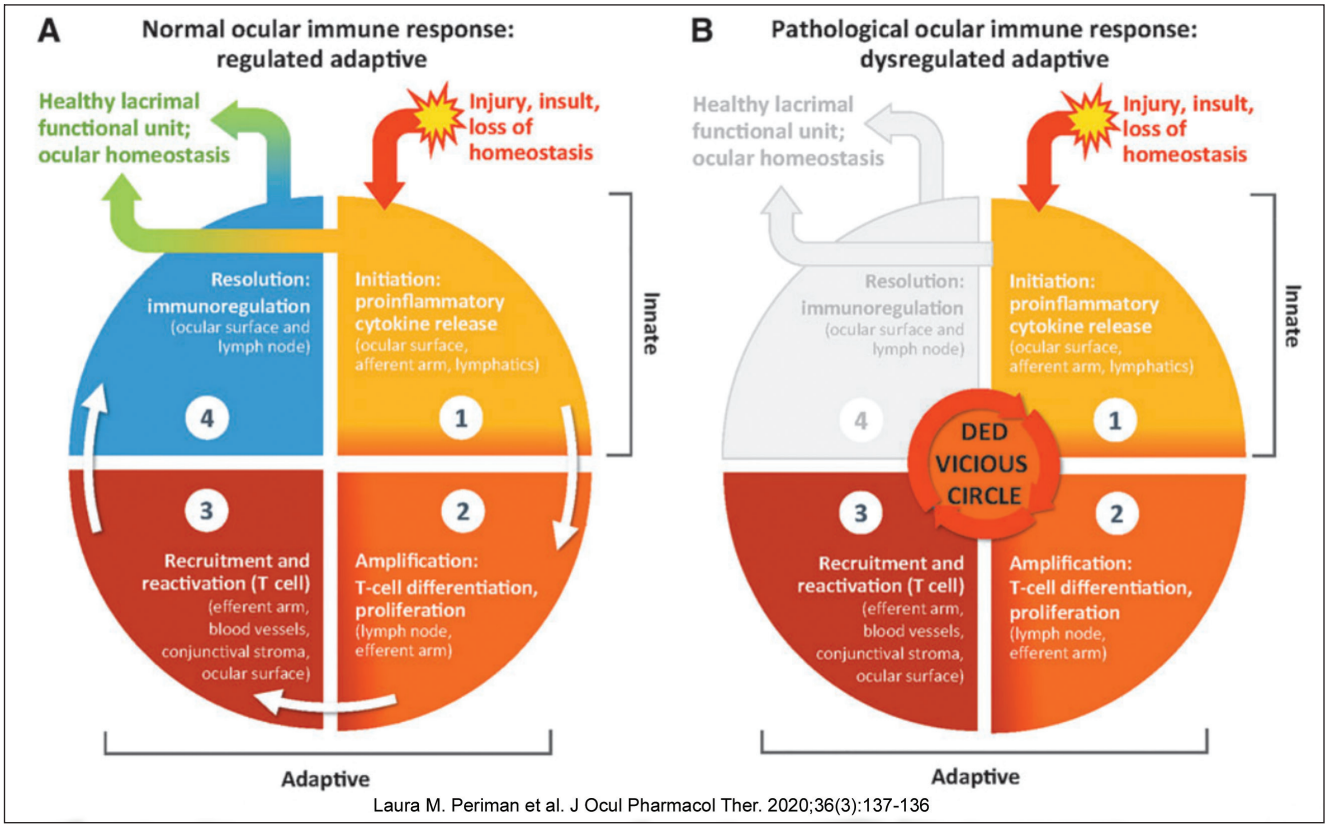


Figure 3. The normal ocular immune response contrasted with the pathological ocular immune response.

DURYSTA™
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For intracameral administration

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IOP=intraocular pressure.
Not an actual patient.

INDICATIONS AND USAGE

DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

Contraindications

DURYSTA™ is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

Warnings and Precautions

The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ 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.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions

In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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

References: 1. DURYSTA™ [Prescribing Information]. Irvine, CA: Allergan, Inc.; 2020. **2.** Data on file, Allergan, 2020. **3.** Standring S. Orbit and accessory visual apparatus. In: *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. 41st ed. Philadelphia, PA: Elsevier Limited; 2016: 666-708.

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DURYSTA™
(bimatoprost implant) 10 mcg
For intracameral administration

Brief Summary—Please see the DURYSTA™ package insert for full Prescribing Information

INDICATIONS AND USAGE
DURYSTA™ is a prostaglandin analog indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

CONTRAINDICATIONS
DURYSTA™ is contraindicated in patients with active or suspected ocular or periocular infections; corneal endothelial cell dystrophy; prior corneal transplantation, or endothelial cell transplants; absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; or hypersensitivity to bimatoprost or any other components of the product.

WARNINGS AND PRECAUTIONS
Corneal Adverse Reactions: The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

Iridocorneal Angle: Following administration with DURYSTA™, the intracameral implant is intended to settle within the inferior angle. DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ 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.

Intraocular Inflammation: Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Pigmentation: Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Endophthalmitis: Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

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

The most common ocular adverse reaction observed in two randomized, active-controlled clinical trials with DURYSTA™ in patients with OAG or OHT was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, and iritis. Ocular adverse reactions occurring in 1-5% of patients were anterior chamber cell, lacrimation increased, corneal edema, aqueous humor leakage, iris adhesions, ocular discomfort, corneal touch, iris hyperpigmentation, anterior chamber flare, anterior chamber inflammation, and macular edema. The following additional adverse drug reactions occurred in less than 1% of patients: hyphema, iridocyclitis, uveitis, corneal opacity, product administered at inappropriate site, corneal decompensation, cystoid macular edema, and drug hypersensitivity.

The most common nonocular adverse reaction was headache, which was observed in 5% of patients.

USE IN SPECIFIC POPULATIONS
Pregnancy: There are no adequate and well-controlled studies of DURYSTA™ administration in pregnant women to inform a drug associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures.

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 1770 times the maximum human bimatoprost exposure following a single administration of DURYSTA™ (based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA™, based plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma C_{max}).

Lactation: There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when DURYSTA™ is administered to a nursing woman.

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

Pediatric Use: Safety and effectiveness of DURYSTA™ in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

PATIENT COUNSELING INFORMATION
Treatment-related Effects: Advise patients about the potential risk for complications including, but not limited to, the development of corneal adverse events, intraocular inflammation or endophthalmitis.

Potential for Pigmentation: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent.

When to Seek Physician Advice: Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

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3. Moderate to severe OSD, poorly controlled inflammation, and undertreated MGD with gland atrophy.

Dr. Gupta: We know that BAK induces conjunctival inflammation and reduces the viability of the corneal epithelial cells. Classic staining persists because the cells are constantly being bathed in BAK and cannot regenerate. TBUT is reduced because the glands become inflamed and atrophy over time. The surface becomes hyperosmolar, starting a vicious cycle of inflammation.

Figure 3 illustrates the normal ocular immune response and what happens when insult, injury, or loss of homeostasis occurs. T-cell activation and recruitment is ramped up, resulting in a cycle of inflammation, and the surface cannot repair itself properly.

Effective management of OSD in our glaucoma patients requires chronic suppression of inflammation, as these patients in particular are susceptible to chronic inflammation, not only because of the molecule—prostaglandins, for example, are pro-inflammatory—but also because chronic exposure to BAK induces inflammation.

When patients have signs and symptoms of dry eye disease in the setting of glaucoma, we should be thinking about prescribing an anti-inflammatory or immunomodulator agent, because these eyes will be chronically inflamed.

We have several agents from which to choose:

- Lifitegrast (Xiidra, Novartis) is an LFA-1 antagonist that blocks interaction with ICAM to stop inflammation. It is FDA-approved to treat the signs and symptoms of dry eye disease. What's unique about this molecule is that it actively inhibits the activation and recruitment of T-cells. Researchers found that in two out of the four clinical studies used to approve Xiidra, patients experienced symptomatic relief as early as 2 weeks,[16] which I attribute to lifitegrast's dual mechanism of action.
- Cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan), which was approved by the FDA 17 years ago, inhibits T-cell activation via modulation of the calcineurin-phosphatase pathway. It has been shown to increase tear production and goblet cell density.[17]
- Cyclosporine ophthalmic solution 0.09% (Cequa, Sun Pharma), FDA-approved in 2018, is a nanomicellar formulation of cyclosporine.[18]

While the use of steroids in patients with glaucoma continues to be controversial, I often prescribe topical steroids for my glaucoma patients who have OSD. It's not advisable for long-term therapy, but I use it for pulse dosing to treat a flare or an exacerbation. We must be cognizant of IOP elevation, cataract formation, and infection risk, particularly in patients who have blebs and other hardware in their eyes. But I think topical steroids when paired with a chronic immunomodulator can have a complementary relationship. I often start these medications side-by-side and use the steroid as induction therapy. That allows time for the immunomodulator to work.

Dr. Radcliffe: I agree that a brief pulse of a steroid is a good way to reboot the system once we've dealt with some offending agent. For example, if I stop a medication after glaucoma surgery and the patient has not yet achieved target pressure, I find a brief period of a steroid helps.

ADDRESSING THE OSD

Dr. Gupta: Like so many patients who are referred to me, this patient had chronic inflammation and moderate atrophy. To address the inflammation, I prescribed lifitegrast twice a day in both eyes. For the MGD, I treated with intense pulsed light (IPL) using the Lumenis M22 laser. I chose IPL because the patient has moderate atrophy and this treatment has a multistep component to it.

IPL employs a non-laser source of broad spectrum light to deliver selective photothermolysis. The light is absorbed in melanin and hemoglobin and is converted into thermal energy, causing selective damage to the telangiectasias along the eyelid. Note that IPL is contraindicated for patients with a skin type above Grade IV on the Fitzpatrick scale.

To perform IPL, we place protective eye shields and apply ultrasound gel before treating from tragus to tragus. I follow the Toyos protocol, which calls for manual gland expression after each IPL treatment.[19] I treat the patient once a month for 4 months and then once every 6 months for maintenance.

IPL can be used to treat a broad range of disease stages from mild to severe, but I especially prefer this as a first choice in patients with significant gland atrophy.

In a 2016 multicenter study, my colleagues and I showed that IPL increases TBUT and oil flow and decreases telangiectasias.[20] Dell and colleagues reported similar results, and they also showed that IPL reduces corneal staining and improves meibomian gland function.[21] Liu and colleagues examined tear samples in patients before and after IPL, and found an altered or improved inflammatory profile in those patients.[22]

In my opinion, IPL is a great treatment for patients, such as this one in our case with moderate disease, as it helps to address inflammation along the eyelid.

Treating meibomian gland obstruction is also important, and in this case, after the series of IPL treatments, we decided to use the Systane iLux MGD Treatment Device (Alcon), which is indicated for adults with chronic disease

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IMPORTANT PRODUCT INFORMATION FOR iLUX® DEVICE

Indication: The iLUX® Device is indicated for the application of localized heat and pressure therapy in adult patients with chronic disease of the eyelids, including Meibomian Gland Dysfunction (MGD), also known as evaporative dry eye.

Contraindications: Do NOT use the iLUX® Device in patients with the following conditions: Patients whose pupils have been pharmaceutically dilated; patients who have undergone ocular surgery within prior 12 months; patients with ocular injury or trauma, chemical burns, or limbal stem cell deficiency (within prior 3 months); patients with active ocular herpes zoster or simplex of eye or eyelid or a history of these within prior 3 months; patients with cicatricial lid margin disease; patients with active ocular infection, active ocular inflammation or history of chronic, recurrent ocular inflammation within prior 3 months; patients with an ocular surface abnormality that may compromise corneal integrity; patients with lid surface abnormalities that affect lid function in either eye; patients with aphakia; or patients with permanent makeup or tattoos on their eyelids.

Warnings/Precautions: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner. The Disposable may not fit all eyes, such as eyes with small palpebral fornices. Use of the iLUX® device is NOT recommended in patients with the following conditions: moderate to severe allergic, vernal or giant papillary conjunctivitis; severe eyelid inflammation; systemic disease conditions that cause dry eye; in patients who are taking medications known to cause dryness; or patients with punctal plugs.

Potential Adverse Reactions: Potential adverse effects may include eyelid/eye pain requiring discontinuation of the treatment procedure, eyelid irritation or inflammation, temporary reddening of the skin, ocular surface irritation or inflammation (e.g., corneal abrasion, conjunctive edema or conjunctival injection (hyperemia)), and ocular symptoms (e.g., burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light).

Attention: Please refer to the User Manual for a complete list of contraindications, instructions for use, warnings and precautions for the iLUX® Device.

References:
1. Alcon data on file, 2019.
2. Alcon data on file, 2019.

Alcon

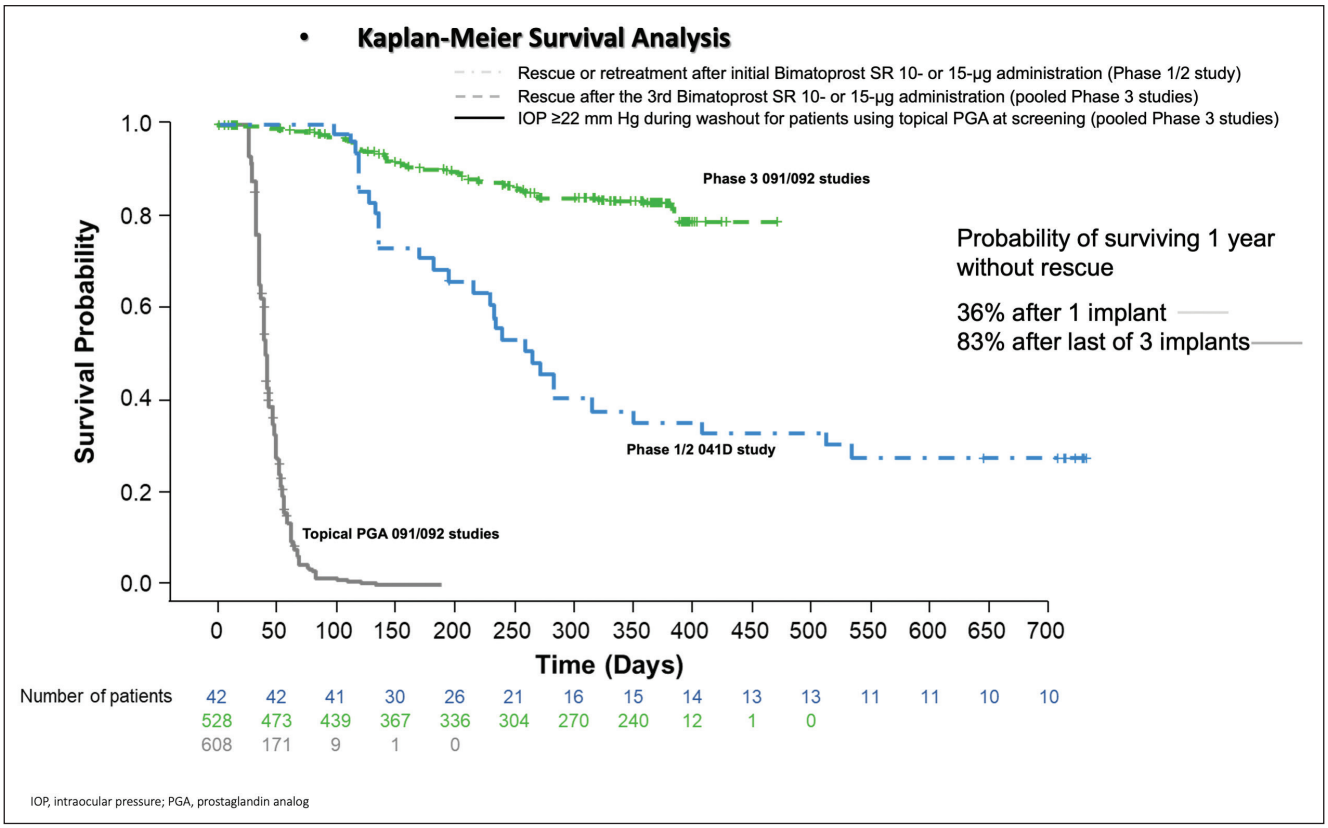

Figure 4. When topical drops are stopped, the efficacy ceases in a matter of days.

of the eyelids. The iLux is a handheld device that applies focal heat and pressure to the eyelids. A magnifier allows direct visualization of the meibomian glands, and the treatment can be titrated. In my practice, I delegate this treatment to a technician.

To help clinicians implement dry eye services, Alcon offers the Dry Eye Excellence Program (DEEP) to physicians using the iLux device. A representative visits your practice to observe your staff and how you're screening patients. I think this program stands out in terms of helping clinicians integrate what they need to optimize efficiency and be successful.

We've now addressed this patient's primary complaint, her ocular surface disease, but her IOP is still not controlled. What should we do about her glaucoma?

SUSTAINED RELEASE IMPLANT FOR POAG

Dr. Radcliffe: In 2020, a new concept in glaucoma therapy was introduced. Bimatoprost SR (Durysta; Allergan) is the first sustained-release, biodegradable, intraocular implant approved by the FDA for the treatment of open-angle glaucoma or ocular hypertension.

The implant, which is about the size of the "I" in the word "LIBERTY" on a dime, is supplied preloaded in a single-use applicator with a 28-gauge needle. The needle enters the anterior chamber where the implant is delivered, settles in the inferior angle, and usually adheres to the trabecular meshwork or against the peripheral inferior iris. The implant elutes drug consistently for 4 months. Made from a biodegradable polymer, the implant hydrolyzes into glycolic and lactic acid and dissolves inside the eye in a year or two.

In phase 1/2 clinical trials, the 10-µg bimatoprost SR implant lowered IOPs 7.4 mmHg through week 16 compared with topical bimatoprost, which lowered IOPs 8.4 mmHg.[23] Retreatment was not required in 91% and 71% of study eyes up to week 16 and month 6, respectively. Adverse events usually occurred within 2 days after the injection and were transient. Conjunctival hyperemia more than 2 days after the injection was more common with topical bimatoprost than bimatoprost SR (17.3% vs 6.7% of eyes).

In phase 3 studies, three implants were administered over a 1-year period.[24] A Kaplan-Meier survival analysis (Figure 4) shows that when topical drops are stopped, the efficacy ceases in a matter of days. In the Phase 1/2 study, one injection of bimatoprost SR 10-µg controlled pressures

in 36% of patients. After treatment with the implant every 4 months for 1 year, 83% of patients maintained target IOPs for 2 years. That's remarkable, and it suggests that this therapy is changing uveoscleral outflow, maybe not permanently but on a lasting basis, so that the efficacy of the drug persists longer than the drug is in the eye.

Because three implants in the eye caused some endothelial cell loss, the current FDA indication is for one injection. I still find plenty of reasons to give one injection, because in some patients, the efficacy will persist for a long time, and some patients need a break from drops that will be meaningful for them.

A candidate for the bimatoprost SR implant must have an open angle and a healthy corneal endothelium. They may have ocular hypertension or glaucoma, may be using any number of topical antiglaucoma medications, and may be phakic or pseudophakic. In my opinion, pseudophakic patients are great candidates, because they will have deep chambers. You won't have to worry about the angle in most cases, and if they've had successful cataract surgery, their cornea is healthy. Other good candidates are patients who have compliance or tolerability issues—red eyes, dry eyes, MGD, a heavy drop burden, difficulty administering drops properly—and whose symptoms can be improved by eliminating topical medications.

CONCLUSION

This patient was treated with the sustained-release bimatoprost implant in both eyes (same-day injections can be given after a betadine prep). Two weeks after receiving the implants, her pressures were reduced to 17 mmHg and 18 mmHg, and eliminating topical agents was of great benefit to her.

I believe intracameral therapy will open up a huge new avenue for glaucoma patients who are suffering from the topical side effects of our standard therapies.

CASE 3: REFRACTORY GLAUCOMA AND BLURRED VISION

Dr. Gupta: This 60-year-old man has a POAG has a history of narrow angles after iridotomies. He reports blurred vision and glare, and fluctuating vision at times. He has been treated with SLT twice, and he uses three topical antiglaucoma medications, including a PGA. His visual acuity is 20/30 OD and 20/40 OS, and his IOPs are 25 mmHg OU. He has early cataracts in both eyes.

MGD is apparent in the clinical photos with some adjacent atrophy. TBUT was 4 seconds.

Dr. Radcliffe: The Cirrus HD-OCT combined report shows early glaucoma in the right eye, a full visual field, obvious cupping, and an inferior RNFL defect. The average RNFL thickness is normal, but don't let that and the normal visual field fool you. This is glaucoma.

The left eye has moderate-to-severe glaucoma with a significant inferior nasal step, possibly some superior changes, diffused RNFL loss and cupping, and an average RNFL thickness of about 65. This is some serious glaucoma.

Thinking about the treatment options for this patient, I know he's using topical medications and has had laser. He's not a candidate for anything in the anterior chamber because of the narrow angles. Other options are tube shunts and trabeculectomy, but I don't think we're there yet. He could be a candidate for the Xen 45 gel stent (Allergan) with mitomycin C, but I want to give his physiologic outflow a chance before I move to Xen. The other category open to us includes the canal procedures. This patient is an excellent candidate for a standalone intervention in that category.

The conventional outflow pathway contributes most of the outflow in normal eyes, and most surgeons prefer to target that pathway first, because of the favorable safety profile.[25-27] Episcleral venous back pressure serves as a backstop that may prevent hypotony postoperatively. We also know the majority of resistance to outflow is at the level of the trabecular meshwork, and bypassing the meshwork and the canal is a good way to address that. In earlier glaucoma—and this is just theoretical—I tend to think there's a healthy outflow system. I just have to get past the trabecular meshwork.

The Omni Surgical System (Sight Sciences) comprehensively addresses the physiologic or conventional outflow system. It combines two distinct angle procedures: ab interno trabeculotomy and viscodilation of the Schlemm canal. It can be used in combination with cataract surgery or as a standalone procedure, and it can be performed to treat early glaucoma, ocular hypertension, or severe glaucoma. By contrast, the trabecular meshwork stents must be paired with cataract surgery and are indicated for mild-to-moderate glaucoma.

Brown and colleagues performed Omni procedures during cataract surgeries on 41 eyes.[28] Eyes with baseline pressures above 21 mmHg achieved up to 9 mmHg of pressure reduction; eyes with lower pressures achieved 4 mmHg or 5 mmHg of pressure reduction (Figure 5).

As a standalone procedure in 13 eyes, the Omni achieved similar efficacy, with a 41% reduction in mean pressure. In the group with higher baseline pressures, the mean reduction was 12.5 mmHg; eyes with lower baseline pressures achieved 6 mmHg of pressure reduction.

The patient and I discussed using the Omni system to perform a standalone procedure, but because he has cataracts and is already going to the OR to treat his glaucoma, he asked us to extract the cataracts at the same time. Before proceeding with cataract surgery, however, we must address the patient's uncontrolled dry eye.

PREOPERATIVE PAUSE TO TREAT OSD

Dr. Gupta: How prevalent is OSD in patients presenting for cataract surgery evaluation?[29] In a study performed by myself and Christopher Starr, MD, we found that 80% of the patients in our study had at least one abnormal test, whether it was MMP-9, osmolarity, or corneal staining. That means, more often than not, a patient sitting in our chair will have OSD.

The ASCRS Cornea Clinical Committee developed an algorithm to assess patients preoperatively (Figure 6). Our goal was to emphasize to cataract and refractive surgeons that OSD negatively impacts outcomes, not only in terms of patients' comfort and visual quality but also in terms of being able to provide optimum refractive outcomes.[30]

For example, we know that high osmolarity or other signs of dry eye disease can lead to abnormalities in keratometry readings. The mnemonic LLPP—look, lift, pull, push—came out of this paper. It is a guided ocular surface examination that should take no more than 30 seconds to perform and will help you more readily identify OSD.

This patient needs OSD management prior to cataract surgery, and now, he's having cataract surgery and a MIGS procedure. Going back to the concept of addressing inflammation and also critically identifying and treating MGD, that's how we considered our treatment options.

In my presurgical patients, I usually use lifitegrast with or without a steroid. In patients who have chronic disease, I have a low threshold to add an immunomodulator, such as lifitegrast, because of its rapid onset of action and also because these patients tend to decompensate postoperatively. We've all had patients who report foreign body sensation

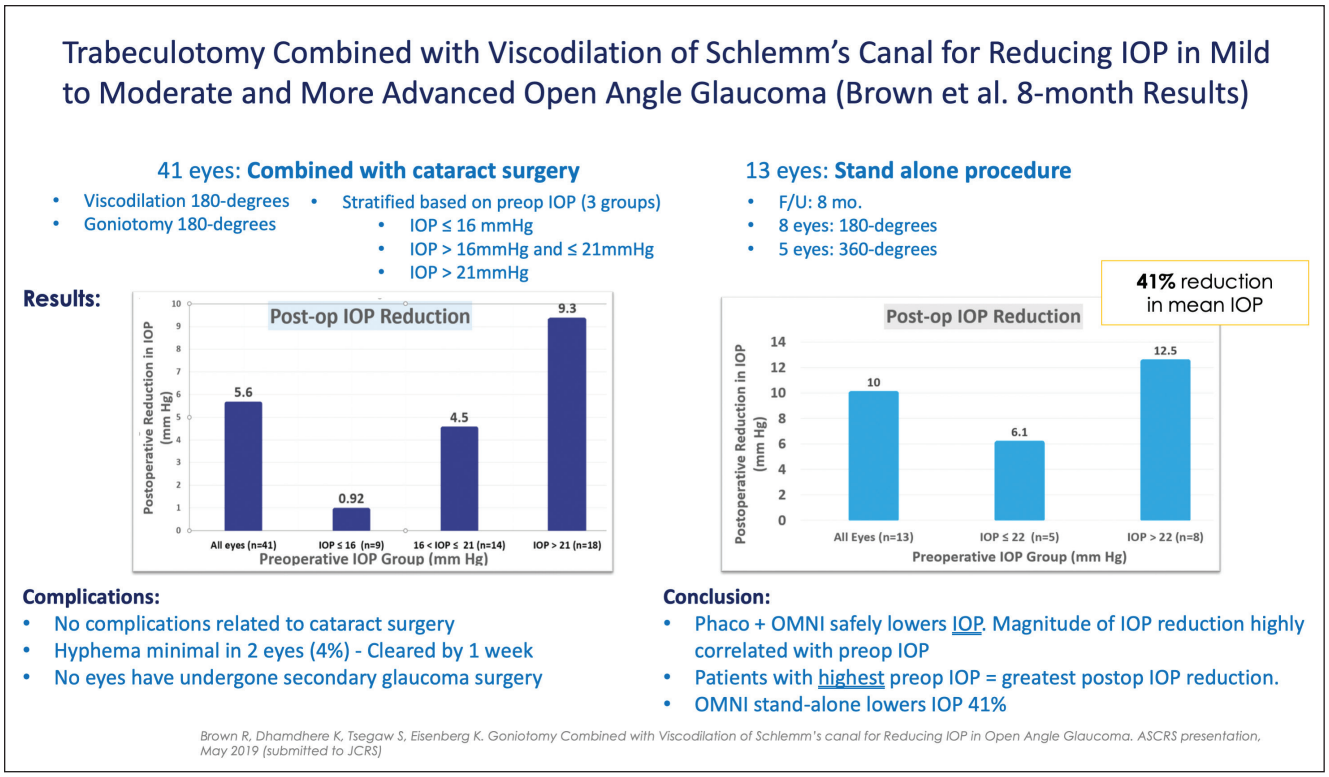

Figure 5. As a standalone procedure, trabeculotomy combined with viscodilation of Schlemm's canal achieved a 41% reduction in mean IOPs.

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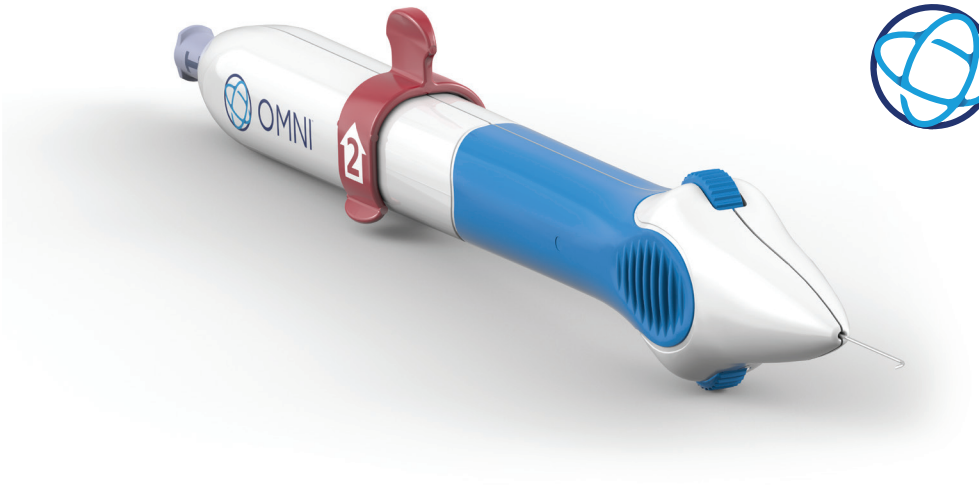

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and irritation after surgery, so by starting lifitegrast or another immunomodulator, I can begin rehabbing the ocular surface even before surgery.

I've found the TearCare (SightSciences) procedure effectively treats MGD in presurgical patients, and it's an easy treatment to integrate into clinical practice. The system consists of flexible eyelid elements that deliver precise, consistent thermal energy. Patients can blink during the 15-minute heating treatment, which helps to express meibum. After the treatment, I express the glands using their proprietary forceps.

The Olympia study, which compared the TearCare procedure with LipiFlow Thermal Pulsation (Johnson & Johnson), found that patients treated with TearCare or LipiFlow showed significant, clinically meaningful improvement in TBUT at 2 weeks and continued to improve at 1 month.[31]

While I want to see anatomic improvement, how the patient feels is of great importance to me, because that's the patient's perception of value. I like recommending this procedure to patients preoperatively because I know they'll experience a rapid improvement not only anatomically but also in terms of their symptoms.

After treating MGD, I bring presurgical patients back to the office to repeat their biometry to detect any changes, and then I perform a basic clinical assessment, including TBUT. It's important to have objective parameters before and after treatment. It's also helpful to share them with patients so they understand what's changing and what's improving. Now that we've teed up the ocular surface, our patient is ready for surgery.

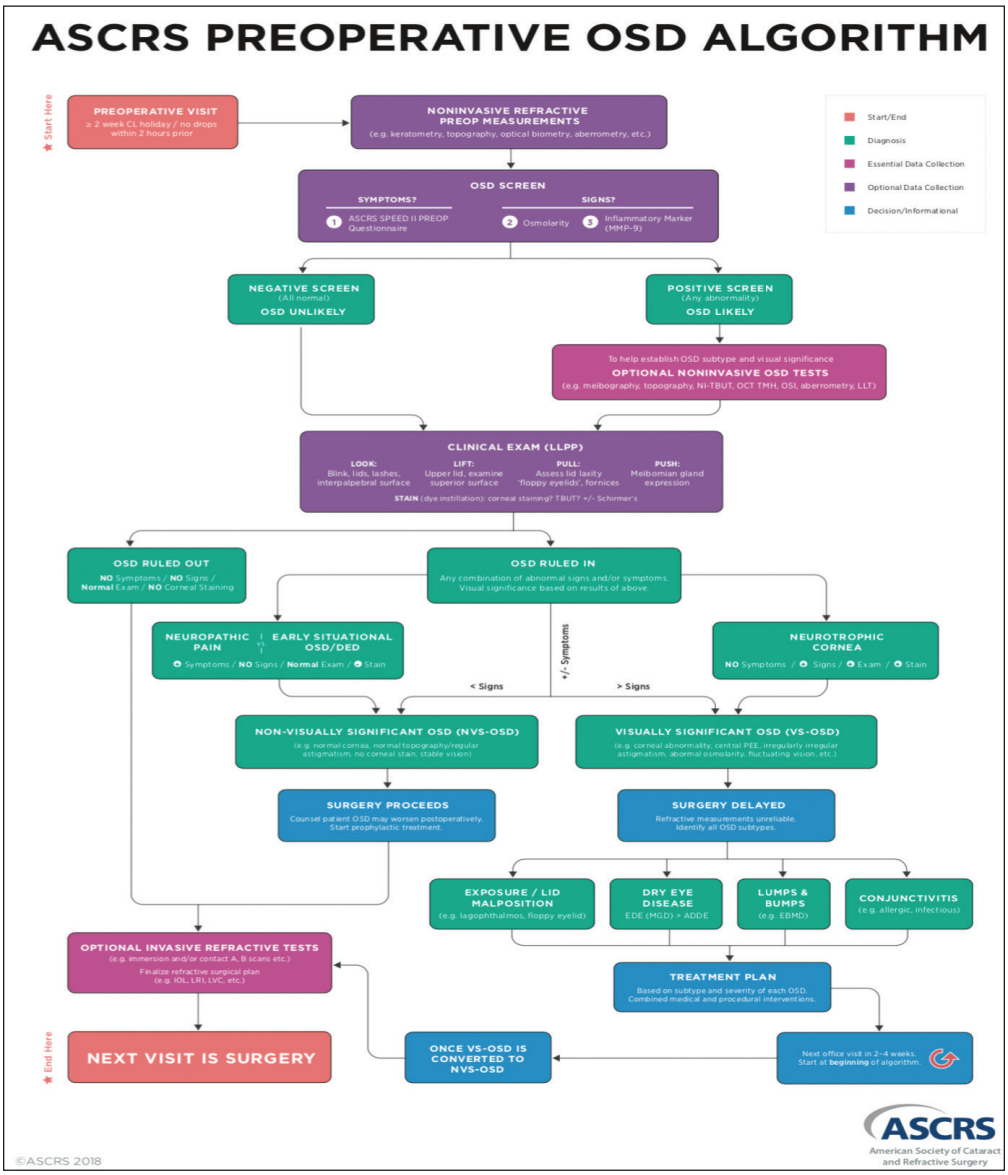

Figure 6. The ASCRS Cornea Clinical Committee developed a consensus-based practical diagnostic OSD algorithm to aid surgeons in diagnosing and treating visually significant OSD before performing refractive surgery.

CONCLUSION

Dr. Radcliffe: Patients like the three we've discussed here are in ophthalmologists' offices every day. They have glaucoma, they're using multiple drops, and they're experiencing the effects of MGD or corneal toxicity. Topical antiglaucoma medications and preservatives have a role in the high prevalence of OSD and dryness in these patients. With new and evolving technologies, we have an opportunity to take action and alleviate these troubling symptoms.

Dr. Gupta: I couldn't agree more. These patients are in

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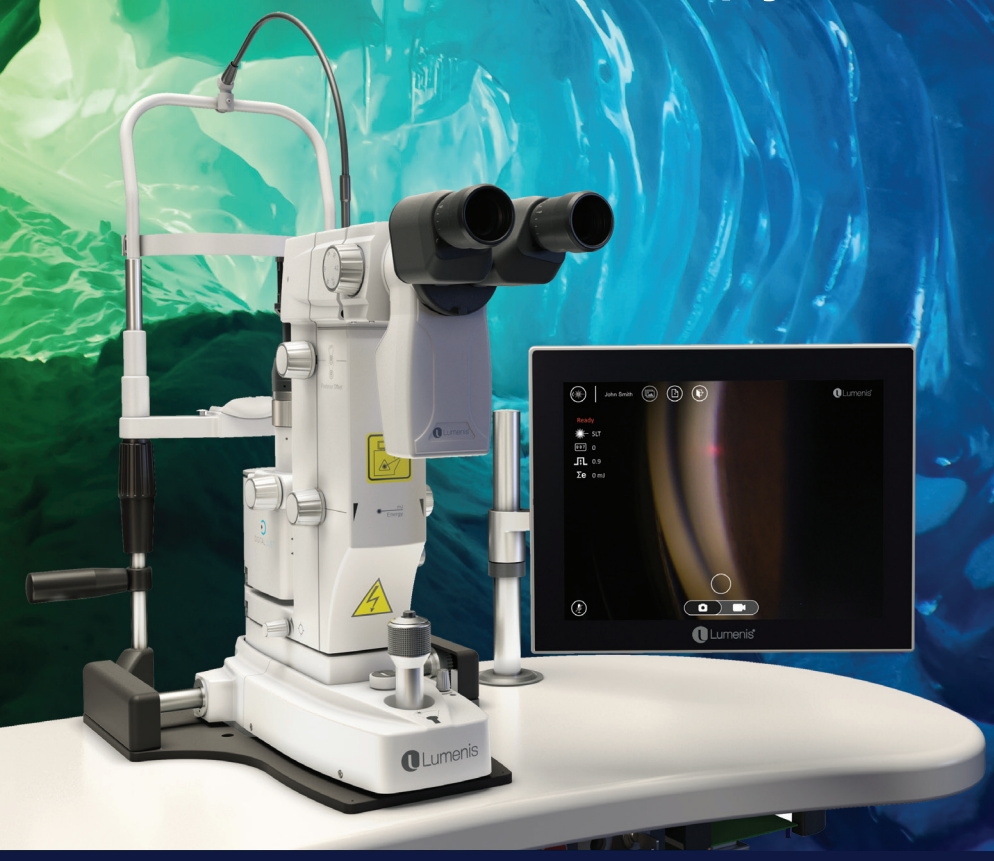

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our practices. You don't have to be a dry eye specialist or a glaucoma specialist. You just have to have patients that need help, and we all have those. We challenge you to adopt some of these new technologies, and, ultimately, help take better care of your patients. ❖

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