

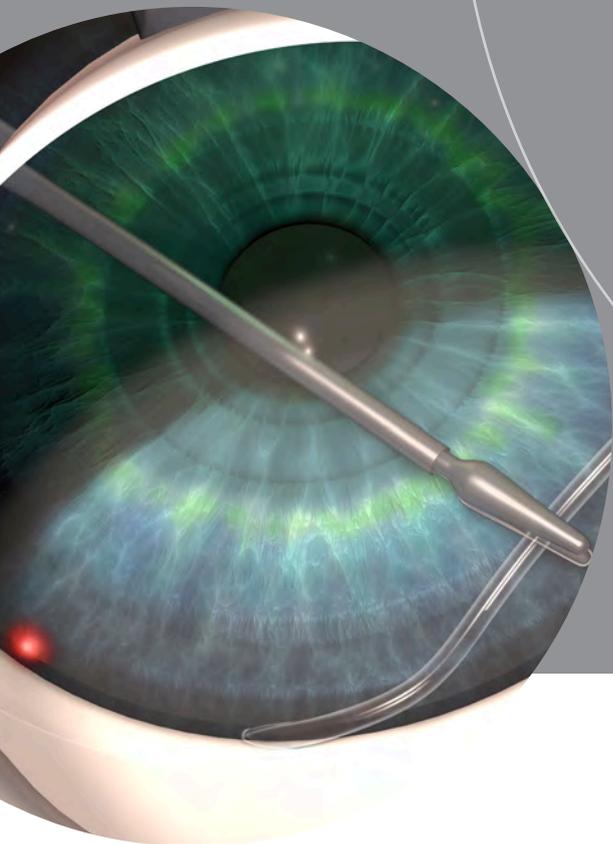


AMERICAN ACADEMY  
OF OPHTHALMOLOGY®

# EyeNet Selections

## Glaucoma 2018

Recent Articles From  
*EyeNet® Magazine*



Protecting Sight. Empowering Lives.®

## RHOPRESSA® (netarsudil ophthalmic solution) 0.02%

Rx Only

### BRIEF SUMMARY

Consult the Full Prescribing Information for complete product information.

### INDICATIONS AND USAGE

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

### DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

### WARNINGS AND PRECAUTIONS

#### 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 previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

#### Use with Contact Lenses

RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

### ADVERSE REACTIONS

#### Clinical Trials Experience

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

#### Corneal Verticillata

Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intraocular administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

#### Animal Data

Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses  $\geq 0.3$  mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on  $C_{max}$ ). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on  $C_{max}$ ).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on  $C_{max}$ ). Malformations were observed at  $\geq 3$  mg/kg/day (1330-fold the plasma exposure at the RHOD, based on  $C_{max}$ ), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on  $C_{max}$ ).

#### Lactation

There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

#### Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years 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

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.



Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

For more information, go to [www.RHOPRESSA.com](http://www.RHOPRESSA.com) or call 1-855-AerieRx (1-855-237-4379).

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043

# Mastering intraocular pressure control with Rhopressa®

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(netarsudil ophthalmic solution) 0.02%

## What makes once-daily Rhopressa® different



**Consistent mean IOP reduction of 5 mmHg** in patients across a range of baseline IOPs<sup>1</sup>



**Once-daily dosing** to simplify dosing regimens<sup>1</sup>



**Mild ocular adverse events** and no known contraindications opens up treatment options<sup>1</sup>



**Unique mechanism of action** for patients who may benefit from improved trabecular aqueous outflow<sup>1</sup>



Visit [Rhopressa.com](http://Rhopressa.com) to learn more about this innovative IOP-lowering treatment.



**Share the Vision** with Aerie Pharmaceuticals—join us at AAO Chicago, Booth 747

### INDICATION AND IMPORTANT SAFETY INFORMATION

#### INDICATION

Rhopressa® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

**Dosage and Administration:** The recommended dosage is one drop in the affected eye(s) once daily in the evening.

#### IMPORTANT SAFETY INFORMATION

**Dosage and Administration:** Twice a day dosing is not well tolerated and is not recommended. If Rhopressa® is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

#### Warnings and Precautions:

**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.

**Adverse reactions:** The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients. The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

**Please see brief summary of full Prescribing Information on the adjacent page.**

#### Reference:

1. Rhopressa Prescribing Information. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017.



[www.aeriepharma.com](http://www.aeriepharma.com)

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US-RHO-P-0128

# The Rhopressa<sup>®</sup> Rocket Tour is headed to AAO!

Introducing Rhopressa<sup>®</sup> (netarsudil ophthalmic solution) 0.02%

## GUEST SPEAKERS

### Robert Fechtner, MD

SUNY Upstate  
Medical University

### Casey Kopczynski, PHD

Chief Scientific Officer  
Aerie Pharmaceuticals

### Jody Piltz-Seymour, MD

Wills Eye Glaucoma Service  
University of Pennsylvania

### Ronald Gross, MD

Southern Eye Group

### Jeffrey Liebmann, MD

Columbia University  
Medical Center

## EVENT DETAILS

Join Aerie Pharmaceuticals and your peers for dinner at the Field Museum

**WHEN:** Saturday, October 27<sup>th</sup>

**REGISTRATION:** 6:30<sup>PM</sup> – 7:00<sup>PM</sup>

**WHERE:** Field Museum  
1400 Lake Shore Drive  
Chicago, IL 60605

**PROGRAM:** 7:00<sup>PM</sup> – 9:00<sup>PM</sup>



**To register for this event, please visit [RocketTourChicago.com](http://RocketTourChicago.com)**

*Limited seating is available.*



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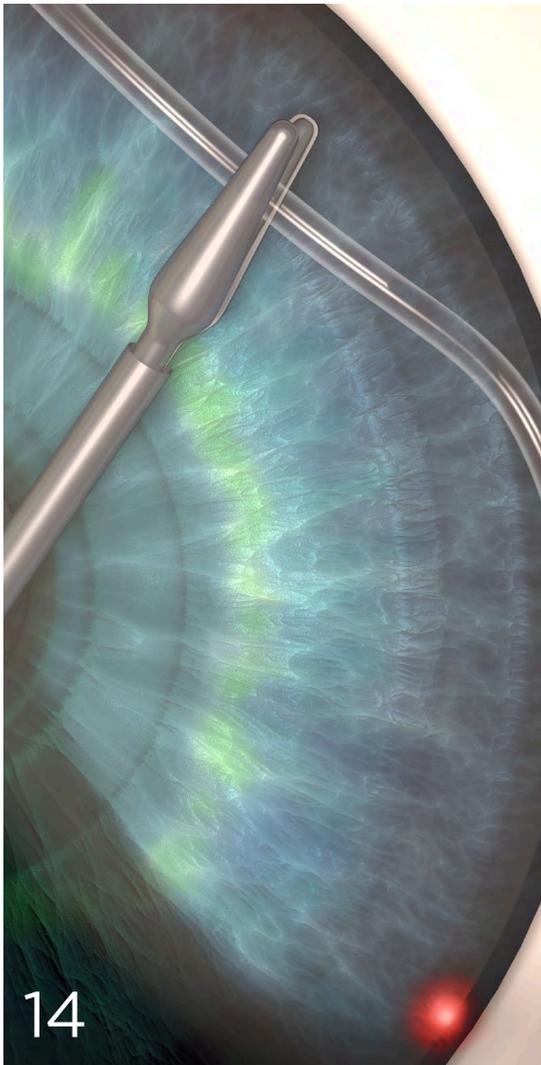
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# EyeNet Selections CONTENTS

REPRINTS FOR  
GLAUCOMA AT AAO 2018  
CHICAGO



## FEATURE

### 14-21 MIGS: Expanding Options for Glaucoma Treatment

The adoption of MIGS procedures and devices continues to grow. Clinicians experienced in their use offer firsthand perspectives and considerations for putting MIGS into practice. *Originally published in February 2018.*

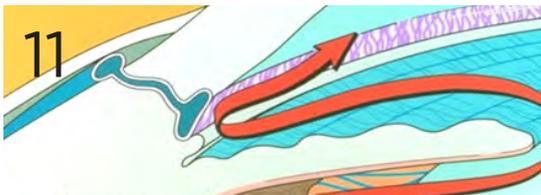
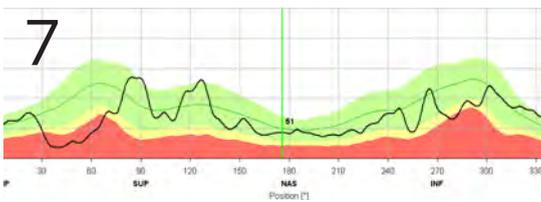
## CLINICAL INSIGHTS

### 7-10 Normal-Tension Glaucoma

Four experts discuss the ins and outs of diagnosing normal-tension glaucoma. *Originally published in June 2018.*

### 11-13 New Drugs

Now that Rhopressa and Vyzulta are here, what can you expect? *Originally published in September 2018.*



COVER ILLUSTRATION  
Alfred T. Kamajian



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# EyeNet Corporate Lunches

*EyeNet® Magazine* helps you make the most of your time at AAO 2018 by bringing you free corporate educational program lunches\* onsite at McCormick Place.

## **Room E353c, Lakeside**

McCormick Place

## **Check-in and Lunch Pickup**

12:15-12:30 p.m. Lunches are provided on a first-come basis.

## **Program**

12:30-1:30 p.m.

## **Programs**

### **Saturday, Oct. 27 Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management**

**Speakers:** Robert Busch, MD (endocrinologist), John W. Kitchens, MD

*Presented by Regeneron Pharmaceuticals, and designed for U.S. retina specialists.*

### **Sunday, Oct. 28 INSiGHTS AT AAO: A Spotlight on Dry Eye Treatment**

**Speakers:** Eric D. Donnenfeld, MD, Edward J. Holland, MD, Terry Kim, MD

*Presented by Shire*

### **Monday, Oct. 29 Cataract Surgery: Life is Beautiful When the Pupil Behaves**

**Speakers:** Eric D. Donnenfeld, MD, Cynthia A. Matossian, MD, FACS, Steven M. Silverstein, MD, Denise M. Visco, MD, Keith A. Walter, MD

*Presented by Omeros Corporation, and designed for U.S. cataract surgeons.*

**Check [aao.org/eyenet/corporate-events](http://aao.org/eyenet/corporate-events) for updated program information.**

\* These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2018 or Subspecialty Day. By attending a lunch, you may be subject to reporting under the Physician Payment Sunshine Act.

# MD Roundtable: Diagnostic Challenges of Normal-Tension Glaucoma

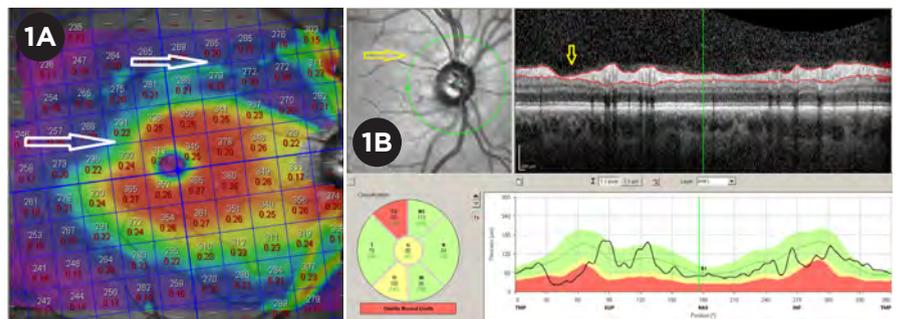
**N**ormal-tension glaucoma (NTG) is a challenging condition with many nuances in diagnosis, monitoring, and treatment. In this first installment of a 2-part series, Sanjay G. Asrani, MD, of the Duke Eye Center in Durham, North Carolina, hosts an MD Roundtable with L. Jay Katz, MD, of the Wills Eye Hospital and Thomas Jefferson University in Philadelphia, Michael S. Kook, MD, of the University of Ulsan and the Asan Medical Center in South Korea, and Kazuhisa Sugiyama, MD, PhD, of Kanazawa University in Japan. The experts discuss the various presentations of NTG and give tips on differential diagnosis. Part 2 of this series, which addresses management of NTG, will appear in the July *EyeNet*.

## The Many Definitions of NTG

**Dr. Asrani:** How do you define NTG in your clinical practice?

**Dr. Sugiyama:** We define NTG as optic neuropathy that progresses despite nonmedicated intraocular pressure (IOP) of less than 22 mm Hg. Otherwise, the clinical features of NTG are similar to those of primary open-angle glaucoma. About 70% of patients with glaucoma in Japan have the normal-tension type.<sup>1</sup>

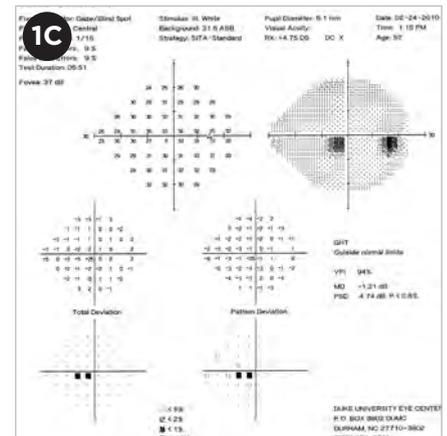
A challenge in diagnosing NTG is that it is nearly impossible to know if



**SEVERAL TESTS.** (1A) The OCT macular thickness map of this patient shows the focal but deep loss of thickness superiorly, along with early affliction of the parafoveal ganglion cell thickness (2 white arrows). (1B) The OCT retinal nerve fiber layer of the same eye shows focal deep loss in the superotemporal area seen in the cross section as well as in the red-free image (yellow arrows). (1C) The visual field of the same eye shows early inferior para-central scotoma.

a patient's IOP is normal all the time. Rather than obtaining diurnal measurements, IOP typically is determined only during office hours. Therefore, instances of high IOP may be missed.

**Dr. Kook:** Traditionally, we define NTG as glaucoma with an IOP of 21 mm Hg and under. This IOP threshold is based on results of a 1958 population-based study using the Schiøtz tonometer and a 2-standard-deviation cutoff.<sup>2</sup> However, this definition has been subject to question, as IOP level



may differ in other populations and when using different tonometers. For example, we demonstrated recently that the mean IOP in a healthy population from the Namil-myon area of South Korea was  $13.3 \pm 2.7$  mm Hg using the Goldmann applanation tonometer.<sup>3</sup> Based on a cutoff of 2 standard deviations from the mean, the threshold for NTG would be an IOP of 18 or 19 mm Hg. I am not sure that defining NTG based on IOP level is clinically helpful. Instead, I find it more useful to differentiate glaucoma based on the underlying risk factors such as IOP-dependent versus non-IOP-dependent type.

Originally published in June 2018.

ROUNDTABLE HOSTED BY **SANJAY G. ASRANI, MD**, WITH **L. JAY KATZ, MD**, **MICHAEL S. KOOK, MD**, AND **KAZUHISA SUGIYAMA, MD, PHD**.

**Dr. Katz:** We apply a similar cutoff to define NTG; we've traditionally used IOP values between 21 and 23 mm Hg in the United States, based on the 2-standard-deviation rule from a mean IOP of 16 mm Hg. However, if we regard NTG as primary open-angle glaucoma that is at least partially dependent on IOP, then we should acknowledge that these cutoffs represent only a limited statistical definition.

There are some sources of measurement error in determining a patient's IOP, such as error associated with corneal thickness. As Dr. Sugiyama noted, we also can miss elevated pressures; study findings have shown that approx-

*"I frequently note focal features in NTG, such as a focal defect in the neuroretinal rim or optic disc hemorrhage that is confined to the inferotemporal or superotemporal region."* —Dr. Kook

imately half of peak IOP levels occur outside of typical office hours.<sup>4,6</sup>

We still apply an IOP cutoff to define NTG, but keep in mind that we manage NTG much as we would high-tension glaucoma: by lowering IOP.

### Know the Presenting Signs

**Dr. Asrani:** Which presenting features support the diagnosis of NTG?

**Dr. Asrani:** As an example, NTG is associated with Flammer syndrome, which involves a constellation of symptoms related to reactive blood vessels and may include difficulty falling asleep, being a high achiever, or having low body mass index (BMI). Other conditions that often accompany NTG are low blood pressure, migraine, and Raynaud syndrome.

**Dr. Katz:** It can be helpful to assess the patient's family history. The results won't necessarily distinguish normal-tension from high-tension glaucoma, but it's a good starting point. I agree that vasospastic disease, such as migraine or Raynaud syndrome, often is associated with NTG. Vasculopathy also seems to correlate with this disease.

The effects of NTG on the visual field (VF) and optic nerve seem to be more focal in NTG than in high-tension glaucoma. For example, with NTG, we see more focal notching, acquired pits of the optic nerve, and disc hemorrhag-

es. And the initial visual field deficits in patients with NTG tend to be denser and perhaps closer to fixation than would be expected in high-tension glaucoma. However, these are trends and not exclusive rules.

**Dr. Kook:** I've found that associations of NTG with some clinical features such as Flammer syndrome may vary between populations. In Korea, for instance, migraine may not be as common as Raynaud syndrome or nocturnal hypotension in patients with NTG. In NTG patients with disease progression despite well-controlled IOP, it is of importance that the clinician rule out nocturnal hypotension due to either

primary vascular dysregulation or secondary to overtreatment with antihypertensive medications. Nocturnal hypotension, particularly associated with overtreatment of systemic hypertension, can be alleviated or prevented in close collaboration with the internist.

In agreement with Dr. Katz, I frequently note focal features in NTG, such as a focal defect in the neuroretinal rim or optic disc hemorrhage that is confined to the inferotemporal or superotemporal region. Cupping in the optic disc tends to be shallow and sloped rather than deep and steep in appearance, and the visual field defects in NTG may often involve the central or paracentral region in the superior hemifield area.

We can attempt to differentiate NTG from primary open-angle glaucoma based on optic nerve appearance or systemic features—although I think it can be quite challenging, as NTG may be on a spectrum of disease having IOP and/or non-IOP risk factors. Some patients with NTG may have clinical features that are very consistent with primary open-angle glaucoma (POAG).

**Dr. Sugiyama:** We see many NTG patients who have sleep apnea. They may have high spikes in IOP and also have hyper- or hypotension at night.

In my experience, several features are more common in NTG than in

POAG. Disc hemorrhage is common in NTG and is a sign of disease progression. This hemorrhage tends to involve a wedge-shaped defect of the retinal nerve fiber layer (RNFL). I have found that NTG also is associated with peripapillary atrophy of the beta zone.

### Recognize Masqueraders

**Dr. Asrani:** Several conditions can masquerade as NTG. Which clinical features make you doubt that it is NTG?

**Dr. Sugiyama:** The disc shape in superior segmental optic hypoplasia (SSOH) is similar to that in NTG. Moreover, both conditions involve focal hypoplasia of the nasal superior sector of the disc and often include a lower visual field defect.

**Dr. Kook:** I agree. SSOH is one of several congenital optic disc anomalies that exhibit localized optic disc changes and present like glaucoma in terms of an RNFL or visual field defect. Others include optic disc drusen, optic nerve pits, and optic nerve hypoplasia.

Myopia is another common condition that can have a presentation similar to glaucoma in terms of clinical features including optic disc and/or RNFL defects or VF deficits respecting the horizontal midline. However, while glaucoma is a progressive optic neuropathy, the natural course of myopia may be different. Optic disc and/or visual field changes associated with myopia may not progress after myopic developmental changes cease in young individuals with a normal IOP level. Optic disc features that are often associated with these young individuals may include optic disc tilt or torsion. In the clinical setting, we should follow up regularly and monitor the glaucomatous-appearing optic disc changes or VF defects found in myopic eyes that may progress over time due to glaucoma or remain nonprogressive due to myopic developmental findings.

Clinical examination of the optic disc is the most important way to differentiate nonglaucomatous masqueraders from NTG. Careful ocular examination can help us determine whether the optic disc has what we call "compatible" glaucomatous cupping, which may traditionally be defined as

increased generalized cupping with vertical cup-to-disc ratio greater than 0.7, and focal loss of the neuroretinal rim with accompanying RNFL defects. For example, vascular changes in the retina, such as hemiretinal or branch retinal vein occlusion, can masquerade as glaucoma in terms of VF changes but do not involve cupping; these retinal vascular abnormalities eventually yield arteriosclerotic vessels.

Imaging modalities such as optical coherence tomography (OCT) also can help us differentiate certain congenital anomalies from glaucoma. Imaging findings that indicate glaucoma may include characteristic superotemporal and/or inferotemporal arcuate areas of pathogenicity. In contrast, findings that suggest congenital optic nerve anomalies often involve thinning of the temporal or nasal side of the RNFL or neuroretinal rim. Inflammatory conditions, including optic neuritis and anterior ischemic optic neuropathy, may also masquerade as glaucoma in terms of clinical presentation but entail lesions of the temporal or nasal side of optic disc in imaging studies.

**Dr. Asrani:** When we use OCT, we look for arcuate patterns closer to the fovea in the macular thickness loss in NTG; the arcuate shape is characteristic of glaucoma rather than the masquerading conditions.

**Dr. Katz:** On examination, it's important to note whether there's asymmetry in the cupping and corresponding asymmetry in the IOP. If so, I would feel comfortable with a glaucoma diagnosis even without strong evidence of visual field loss because structural ocular changes often precede functional ones.

We don't want to miss serious issues that mimic glaucoma. Certain findings would be atypical for NTG in the United States: young age; central visual acuity losses; a cecentral scotoma, rather than the arcuate or paracentral defects more typical of glaucoma; visual field loss that respects more of the vertical midline; and optic nerve pallor greater than cupping. Such findings might prompt further workup, including magnetic resonance imaging of the head and orbits to detect etiologies

involving the central nervous system (CNS).

We also would consider optic neuropathies unassociated with IOP, such as those due to toxic, drug-related, or nutritional conditions. We used to perform imaging of the head frequently to evaluate NTG. Today, imaging is reserved for these more atypical features—with CNS imaging, we tend to find in patients with typical features of glaucoma only small vessel disease indicative of mild systemic vasculopathy.

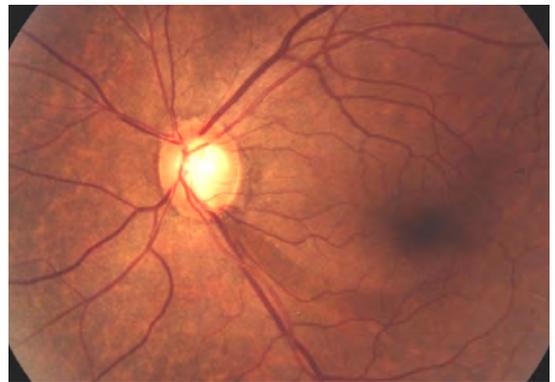
A clinical exam is vital and can reveal findings that can't be obtained with imaging alone. The retina and optic nerve should be examined carefully. You should evaluate pallor in the optic nerve; if the amount of pallor exceeds the amount of cupping, the etiology may be nonglaucomatous. You should also consider the vasculature, as small branch retinal vein occlusion, embolic plaques, or a slowly advancing retinal detachment can masquerade as progressive visual field change.

Certain blood tests can be performed to rule out masquerading conditions. If we find pallor of the optic nerve during clinical examination, we usually order a complete blood count to test for profound blood loss or anemia. Hypotension combined with anemia can result in ischemic changes. In a workup for inflammatory diseases that may mimic NTG in presentation, I would determine the erythrocyte sedimentation rate and the level of C-reactive protein.

**Dr. Asrani:** In terms of blood tests, I typically order the fluorescent treponemal antibody absorption test (FTA-ABS) for neurosyphilis. I also request measurement of B<sub>12</sub> levels because a deficiency of vitamin B<sub>12</sub> sometimes masquerades as NTG.

**Dr. Sugiyama:** In Japan, high myopia is prevalent and involves a disc shape akin to that of NTG. We have to be careful in the differential diagnosis, and visual field testing is crucial for this.

Patients with NTG usually have upper or lower visual hemifield defects and the fixation point is spared until late



**FUNDUS PHOTO.** This image shows a focal loss of the retinal nerve fiber layer inferiorly, extending into the parafoveal region (dark band extending from disc at 5 o'clock position).

stage. In patients with high myopia and glaucoma, the fixation point is often affected at an early stage of visual field loss; frequently, the first obvious stage that we observe is deep scotoma close to the fixation point. We call this an early-stage central visual field loss. Close monitoring of these patients is key.

**Dr. Asrani:** A typical feature of NTG is paracentral visual field loss that does not involve central acuity. I find that OCT results of patients with NTG indicate arcuate patterns accompanied by losses of paracentral ganglion cell groups—these losses occur at an earlier stage than in high-pressure glaucoma.

### Consider Systemic Factors

**Dr. Asrani:** Have you noticed an association of low body mass index and/or low cerebrospinal fluid (CSF) pressure and NTG?

**Dr. Kook:** Patients diagnosed with NTG often have low BMI and low CSF pressure. Dr. Ningli Wang and colleagues demonstrated an association of CSF pressure with IOP in NTG.<sup>7</sup> Their work was based on the hypothesis that pressures in the arterial system, CSF compartment, and intraocular space are related. Theoretically, low CSF pressure could produce an elevated translaminal pressure gradient and result in NTG despite normal IOP. However, I don't know the frequency of this phenomenon, and I do not presently use this concept in clinical practice. Moreover, currently, there is no gold standard for accurately measuring CSF pressure as well as IOP



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in our habitual-body position.

**Dr. Katz:** The idea that people who have high BMI are more protected from glaucoma is interesting to me, but I wouldn't incorporate this into clinical practice. The association of low BMI and NTG underscores the complexity of this disease. We know that IOP is important, but there are additional contributors. The translaminal pressure gradient seems to be another stress factor involved in development of NTG. However, it's challenging to measure CSF pressure accurately, and even if we can determine this pressure, how would we change therapy?

Blood pressure seems to be another pressure factor in NTG. Glaucoma prevalence is higher among patients with low diastolic blood pressure.<sup>8</sup> These 3 pressure components might be important in the development of NTG and may have contributions that vary on an individual level.

Another potential component is metabolic dysfunction—whether mitochondrial or otherwise. A metabolic abnormality could result in excessive cell death signals and/or a lack of cell-survival signals that could lead to death of retinal ganglion cells.

## Other Diagnostic Enigmas

**Dr. Asrani:** *I have treated patients with NTG who subsequently develop high-pressure glaucoma. In these patients, the glaucoma suddenly and dramatically worsened. During examination, I have observed intermittent angle closure or chronic angle closure in many of these patients. These conditions cause high spikes in IOP. Even if you treat the compounding problem by cataract extraction or laser iridotomy, the residual NTG remains.*

**Dr. Katz:** Glaucoma has several diagnostic enigmas. One is burned-out pigmentary glaucoma, in which the patient loses some pigmentary dispersion features but no longer has elevated IOP.

Some patients may have had steroid-induced pressure elevation, but by the time you see them, they are off the steroids; they have definite optic nerve deterioration and visual field loss, but IOP is no longer elevated.

**Dr. Sugiyama:** I agree with Dr. Asrani;

intermittent acute angle-closure glaucoma is an important consideration in the differential diagnosis of NTG. Another problem of measuring IOP is corneal thickness. If the center of the cornea is very thin, this can result in underestimation of IOP.

Another diagnostic challenge relates to Posner-Schlossman syndrome. These patients can present with NTG but also may have spikes in IOP.

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See disclosure key, page 5. For full disclosures, view this article at [aao.org/eyenet](http://aao.org/eyenet).



**MORE ONLINE.** Part 2 of this two part series appeared in July 2018. Look for it at [aao.org/eyenet/archive-back-issues](http://aao.org/eyenet/archive-back-issues).

## Drug Update: Vyzulta and Rhopressa

**A**fter an extended drought, 2 new—and much anticipated—glaucoma drugs are now on the market. “We’ve had a long stretch without any new glaucoma medications,” said Ahmad A. Aref, MD, at the University of Illinois College of Medicine in Chicago. “Now, at the same time, we have 2 relatively low-risk ways to decrease the threat of irreversible vision loss from glaucoma. That’s a big deal.”

In late 2017, the FDA approved latanoprostene bunod ophthalmic solution (Vyzulta, 0.024%; Bausch + Lomb) and netarsudil ophthalmic solution (Rhopressa, 0.02%; Aerie Pharmaceuticals) for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.<sup>1,2</sup> “Rhopressa and Vyzulta have stolen the limelight,” said Dr. Aref. “It will be interesting to see how this plays out, especially from a payer perspective.”

Here’s a look at the 2 drugs, plus an update on drugs in the pipeline (see “From Drought to Flood?” on page 28).

### Vyzulta: Releasing Nitric Oxide

A once-daily eyedrop, Vyzulta is a prostaglandin analog that is metabolized into 2 moieties and regulates IOP through both the trabecular outflow and uveoscleral outflow pathways, said Robert N. Weinreb, MD, at the Univer-

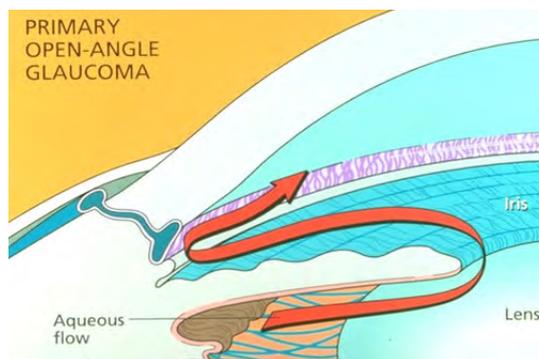
sity of California, San Diego.

**Dual mechanism of action.** “One component is latanoprost, our most efficacious first-line agent for glaucoma, which has been on the market for more than 2 decades and removes fluid through the uveoscleral outflow pathway,” said Dr. Aref.

The second component is butanediol mononitrate, which releases nitric oxide (NO), Dr. Weinreb said. “Nitric oxide induces cell relaxation in the trabecular meshwork by activating the nitric oxide–cyclic guanosine monophosphate signaling pathway, which is thought to lead to a widening of the intercellular spaces in the trabecular meshwork, thereby increasing the conventional outflow.”

The NO component is the unique aspect of the drug’s mechanism of action, giving it a bit of an efficacy edge in lowering IOP over latanoprost alone, said Dr. Aref. When different concentrations of Vyzulta were compared against latanoprost alone,<sup>3</sup> only higher concentrations of Vyzulta were found appreciably more effective, he said. “This suggests that the nitric oxide was responsible for the incremental efficacy.”

**Efficacy.** A veritable space race of studies has examined the effectiveness



**METHOD OF ACTION.** Through novel mechanisms, both Vyzulta and Rhopressa improve outflow of aqueous through the trabecular meshwork. Each medication is a once-daily eyedrop.

and safety of Vyzulta. Results of the LUNAR and APOLLO studies showed that Vyzulta was more effective than timolol. Although the findings were not a surprise, the noninferiority study was necessary, said Harry A. Quigley, MD, at the Wilmer Eye Institute in Baltimore. “Before bringing a glaucoma drug to market, the FDA requires that it work at least as well as timolol.”

A study published earlier this year<sup>4</sup> also looked at the pooled results of all studies comparing Vyzulta to timolol over 12 months, said Dr. Aref. “With Vyzulta, the percentage reduction in IOP from baseline was 32%. That’s a sizable reduction with just 1 eyedrop dosed once a day.”

The VOYAGER study compared Vyzulta to latanoprost alone. Among the Vyzulta studies, Dr. Aref considers it most significant because latanoprost is the clinical benchmark against which other glaucoma drugs are compared. In this study, Vyzulta was associated on

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BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING AHMAD A. AREF, MD, HARRY A. QUIGLEY, MD, AND ROBERT N. WEINREB, MD.

average with 1.2 mm Hg of additional IOP lowering compared to latanoprost.<sup>3</sup>

“This is fairly significant,” said Dr. Aref, “because epidemiologic studies have shown that for every 1 mm Hg incremental decrease in IOP, you can reduce the risk of visual field loss related to glaucoma by about 10%.”

Other studies have also looked at 24-hour lowering of IOP, said Dr. Weinreb, indicating that Vyzulta is effective both day and night.<sup>5</sup>

**Safety and tolerability.** “In a phase 2 clinical trial, Vyzulta was very similar to latanoprost in terms of tolerability,” said Dr. Weinreb. Most side effects, such as irritation and eyelash changes, were mild, and hyperemia was similar in both groups. “But, of course, the drug is only recently available,” he said.

Indeed, wider clinical use may eventually uncover issues with Vyzulta, as has happened with other ophthalmic drugs. Dr. Quigley cited timolol as a case in point: Individuals with dry eyes were not admitted to the study, he said, but once the drug came out of controlled trials into the real world, beta-blockers were found to be challenging for people with dry eyes.

**Role for Vyzulta.** Vyzulta is appropriate as a first-line treatment option for patients with open-angle [glaucoma] or ocular hypertension, Dr. Weinreb said. Many patients may also be put on Vyzulta as a second-line therapy in an attempt to avoid surgery, Dr. Quigley said. “If you tell patients they have to take this new drug or have surgery, you’ll likely increase their adherence.”

### Rhopressa: First ROCK Inhibitor

Like Vyzulta, Rhopressa is a once-daily eyedrop. However, as a Rho kinase (ROCK) inhibitor, it represents the first new class of glaucoma drugs in more than 20 years.

**Triple mechanism of action.** Rhopressa possesses 3 different mechanisms of action in a single agent, said Dr. Aref. The drug lowers the resistance to outflow through the trabecular meshwork, he said. Rhopressa also decreases production of fluid and decreases episcleral venous pressure.

Among its effects, Rhopressa works at the cellular level within the trabecu-

lar network, and it has a novel mechanism of action there, said Dr. Weinreb. “The drug decreases actin-myosin contraction and reduces actin stress fibers and focal adhesions in the trabecular meshwork to improve the outflow of aqueous humor.”

**Efficacy.** ROCK inhibitors are supported by extensive basic science research showing improvement of outflow through the trabecular meshwork, predominantly for glaucoma patients with higher-than-normal pressures, said Dr. Quigley, but they may also be effective for those with lower pressures. Few studies have examined those with pressures below 20 mm Hg at the time of diagnosis, he said, which is about half of those who have open-angle

glaucoma with optic nerve damage.

However, noninferiority timolol studies—ROCKET-1 and ROCKET-2—included lower pressures in their study groups.<sup>6</sup> These studies found timolol was not better than Rhopressa for patients with baseline eye pressure less than 25 mm Hg over a 3-month time period, said Dr. Aref. “Rhopressa showed consistent IOP reduction, about 5 mm Hg across a range of baseline pressures,” said Dr. Weinreb, “particularly notable in patients with low baseline IOP.”

**Safety and tolerability.** In ROCKET-1 and ROCKET-2, about half the patients experienced conjunctival hyperemia, the most common side effect. This redness may result from one

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## From Drought to Flood?

Here’s a sample of drugs and devices in the glaucoma pipeline.

**Roclatan.** In May, Aerie filed a new drug application to the FDA for Roclatan, its once-daily combination of netarsudil and latanoprost. “That could be very attractive, because the fixed-dose combination has performed significantly better than either netarsudil or latanoprost alone,” said Dr. Weinreb.

“To help with the adherence issue, we’ve wanted to see drugs combined with latanoprost for a long time,” Dr. Quigley commented. “This could be beneficial for those who need more than the prostaglandin alone.” The drug is definitely needed, added Dr. Aref. “It might be a very good first-line option for our patients. The big question is whether the combination agent is more efficacious than Vyzulta.”

**Sustained-release options.** In trials under highly controlled conditions, patients only use 72% of their topical glaucoma medications, said Dr. Quigley, but the estimate in the real world is closer to 50%. If clinicians could deliver a sustained-release drug in the office that lasted 6 months, he said, “it would only have to be half as effective as the eyedrop to be more effective overall. And it would also be there in a constant dose instead of in a whopping high dose followed by none at all 24 hours later.” Because sustained-release drugs do sacrifice efficacy to some degree, they may not be a first-line therapy for those without adherence issues, said Dr. Aref.

In preclinical studies, Dr. Quigley and his colleagues have experimented with subconjunctival delivery of biodegradable polymer microparticle formulations of dorzolamide. “Other research is ongoing with a variety of methods for sustained delivery,” he said.

Allergan has a biodegradable sustained-release bimatoprost implant in clinical trials that is injected into the anterior chamber, said Dr. Weinreb. An ongoing phase 3 clinical trial may answer questions about its length of efficacy and impacts on the cornea.

**Microdose spray.** A new technology by Eyenovia uses a variation on high-resolution inkjet printing technology that allows patients to self-administer small doses of drug to the eye, said Dr. Weinreb. This has the potential to reduce side effects and increase safety and tolerability, he said, adding that the company is planning phase 3 studies.



of Rhopressa’s mechanisms of action, which is relaxation of the blood vessels, said Dr. Aref.

During the drug’s early days on the market, Dr. Quigley expected reports of redness to be more substantive than those noted during the clinical trials, as trial participants tend to be less tolerant of side effects. “If you have lots of redness in phase 2 and 3 trials, it won’t get better once the drug is used in the real world,” he said.

But now that Rhopressa has been in use for several months, “the redness issues have been much less than what I would have expected from clinical trial data,” Dr. Aref said. “I currently let patients know to expect some degree of redness that will likely wane over the first few weeks of therapy. That expectation allows patients to tolerate the agent a little better. In practice, it is unlikely for patients to discontinue therapy for this reason alone.”

Other common side effects noted during clinical trials were discomfort with drug administration and conjunctival hemorrhage—typically mild petechiae at the limbus, said Dr. Weinreb. “Twenty percent of patients also experienced corneal verticillata. This side effect does not seem to affect vision and is reversible with discontinuation of the drug.”

Dr. Quigley raised concerns about the safety of drugs like Rhopressa that alter the sclera. Do they have an impact on retinal ganglion cell axons? “It is extremely important to ensure that any negative effect is negligible or that the alteration is potentially beneficial to the ganglion cells,” he said. “However, we worried about the same thing with latanoprost, and after 20 years, there is no indication that the protective effect of IOP lowering is lessened by a detrimental effect that increases glaucoma damage.”

**Role for Rhopressa.** “Rhopressa is likely to be a useful second-line treatment,” said Dr. Weinreb. “It is not quite as effective as the prostaglandins and might not be as well tolerated.” However, secondary types of glaucoma, such as steroid-induced glaucoma, may be amenable to Rhopressa because of its unique mechanism of action,” Dr.

Aref noted. “Steroids increase resistance to outflow through the trabecular meshwork, but Rhopressa works to decrease it.”

### A Note on Cost

When Vyzulta initially entered the market, Dr. Quigley said, his office staff was spending “a lot of time and effort” trying to get the drug for patients, as most pharmacy plans did not cover it at that point.

But coverage and reimbursement are active processes, and costs are shifting rapidly. For instance, in late June, Rhopressa was added to the preferred panel for a major plan, and the price fell to \$25 per bottle for those patients.

Even as more drug plans add Vyzulta and Rhopressa, cost will be a critical issue for clinicians to discuss with their patients. In particular, the cost differential between Vyzulta and latanoprost—which has been a generic agent for about 5 years—may need to be part of the conversation, Dr. Aref noted.

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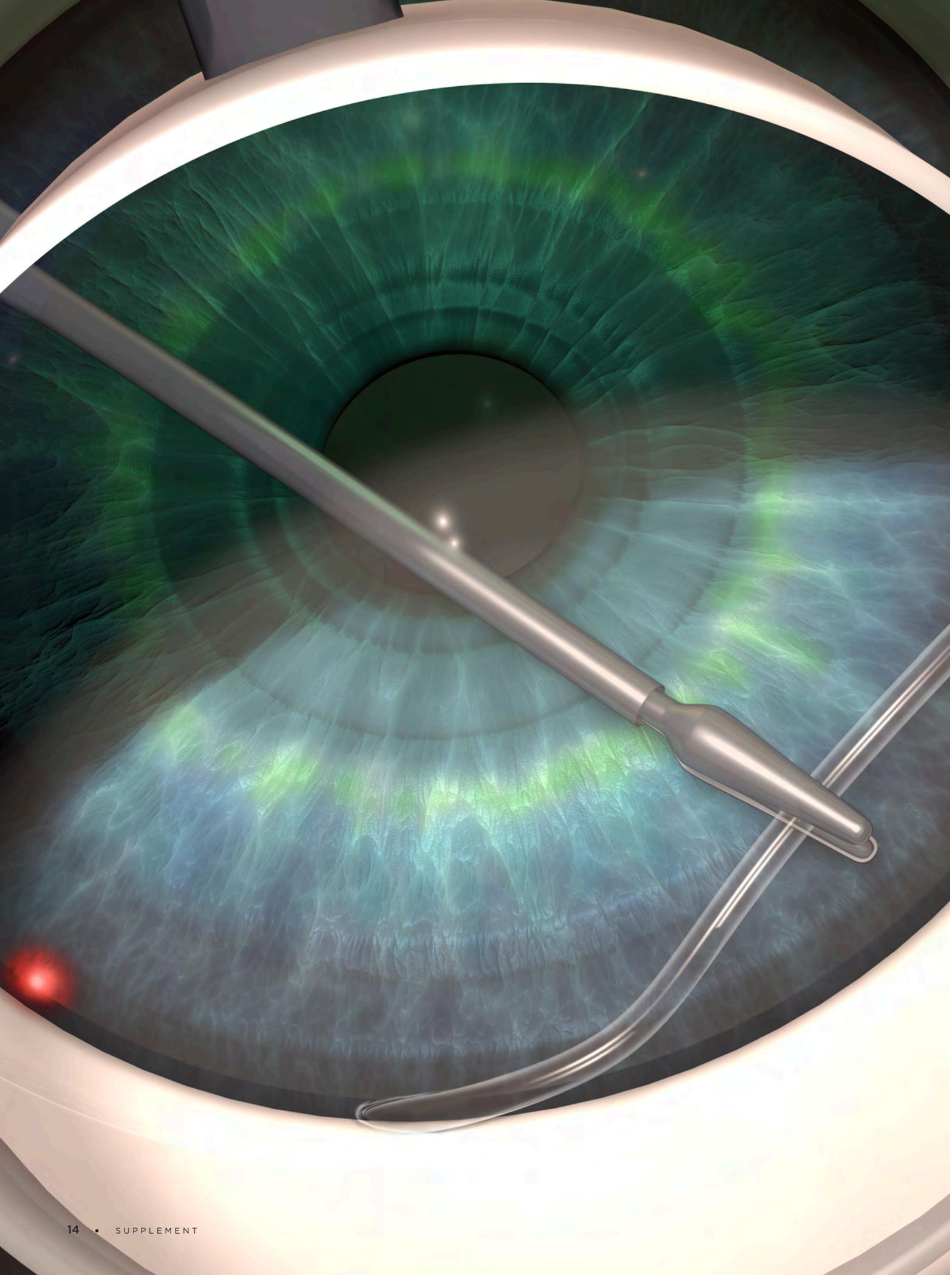
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# MIGS:

## Expanding Options for Glaucoma Treatment

As the uptake of MIGS continues to increase,  
early adopters share their perspectives and practices.

By Lori Baker-Schena, MBA, EdD, Contributing Writer

In the decade since Iqbal Ike K. Ahmed, MD, coined the term *microinvasive glaucoma surgery*—better known as MIGS—the field has grown exponentially.

Dr. Ahmed noted several reasons for the growing interest in MIGS: “Compliance is really poor in glaucoma patients, and even if the patient is compliant, quality of life and the high costs of medicine continue to be issues. We must continually look for solutions for these patients. MIGS are moving in that direction,” said Dr. Ahmed, who is a glaucoma specialist with the Prism Eye Institute in Mississauga, Ontario, Canada.

An online survey of glaucoma surgery practice preferences conducted by the American Glaucoma Society found that among patients who had initial surgery for primary open-angle glaucoma (POAG), the percentages were 59% for trabeculectomy with mitomycin C (MMC), 23% for a glaucoma drainage device (GDD), and 14% for MIGS. When the glaucoma procedure was combined with cataract surgery, the percentages were as follows: trabeculectomy with MMC, 24%; MIGS, 22%; and GDD, 9%.<sup>1</sup>

The survey also found that iStent and Trabectome were the most commonly used MIGS procedures in 2016.

### Debating the Role of MIGS

Although multiple studies have associated MIGS with a favorable safety profile and modest efficacy, others cite a lack of evidence in proving the effectiveness of these techniques.

In response to “good, healthy skepticism” from some quarters, Dr. Ahmed said that “MIGS have been very well studied for many years, with a wealth of published data.” He emphasized that MIGS are not designed to replace trabeculectomy in advanced glaucoma. Rather, “Surgeons are using MIGS procedures in their mild to moderate patients who need lower intraocular pressure (IOP) but in whom they are reluctant to operate because of the side effects associated with trabeculectomy.”

### The Case for MIGS

Glaucoma specialist John P. Berdahl, MD, with Vance Thompson Vision in Sioux Falls, South Dakota, said he considers the entire range of MIGS options when tailoring treatment for his glaucoma patients.

**Fitting the procedure to the patient.** “It is my duty to fit the procedure to the patient,” Dr. Berdahl noted. “That being said, when you are first starting out with MIGS, it is good to get comfortable with one procedure and then expand out to other procedures because there are a lot of similarities.” He added that the learning curve for a MIGS procedure is between 10 and 20 cases.

Dr. Berdahl discussed his 3-year results from patients who had an iStent implanted in combination with cataract surgery.<sup>2</sup> “This approach effectively lowered IOP in open-angle glaucoma (OAG) patients from a mean of  $19.13 \pm 6.34$  mm Hg to  $15.17 \pm 3.53$  mm Hg after 2 years,” he said. “Interestingly, we found that the magnitude of IOP reduction was more significant in patients

with higher preoperative pressure and also that medication use was significantly reduced.”

**An “early adopter’s” experience with iStent.** Glaucoma specialist Mark J. Gallardo, MD, of El Paso Eye Surgeons in Texas, is an “early adopter” of several MIGS procedures, an interest fueled by his desire to provide patients with the most advanced technology, especially if it proves safer, with a quicker recovery.

Dr. Gallardo believes that the modest results from the early clinical trials of the iStent do not reflect the full potential of this approach, as the trial investigators were the first in the world to use the device in a clinical setting and had minimal experience in the best placement. He noted that 70% of the stents were implanted by surgeons who had performed 5 or fewer procedures.

“The learning curve, as well as the previous lack of knowledge on how to maximally manipulate the outflow system with targeted stent implantation, adversely impacted the data,” he said.

**Placement and patients.** Ultimately, surgeons,

including Dr. Gallardo, learned that targeting areas adjacent to collector channels could enhance the efficacy of the stent. Intraoperative visual cues, such as increased regurgitation of blood (blotching) within Schlemm’s canal or increased areas of pigmentation on the posterior trabecular meshwork, help to highlight the location of patent collector channels.

“This, coupled with our identification of ideal candidates for the procedure—those already on 1 to 3 glaucoma drugs with IOP targets in the mid-teens range—have led to results superior to those of the pivotal trial, and subsequent research has demonstrated the safety and effectiveness of the trabecular microbypass stent [iStent],” he said.

**Case series shows benefits.** Dr. Gallardo conducted a retrospective case series in a predominantly Hispanic patient population with moderate to severe glaucoma to assess reduction of IOP and/or medication burden at 12 months following implantation of 1 trabecular microbypass stent during cataract surgery.<sup>3</sup>

## A MIGS Primer

MIGS procedures share 5 key characteristics<sup>1</sup>:

- Ab interno microincision through a clear corneal approach, allowing MIGS to be performed easily in conjunction with cataract surgery; providing a direct view of the angle; and avoiding conjunctival scarring, in case later glaucoma surgery is required.
- Minimal trauma, maintaining normal ocular anatomy and function as much as possible.
- At least modest efficacy, making them a reasonable option in selected patients.
- Favorable safety profile, avoiding the serious complications seen with traditional surgeries, including bleb infections, hypotony, and corneal decompensation.
- Rapid recovery.

### Implanted MIGS

Stent devices fall into 3 main categories:

#### 1. Increasing trabecular outflow:

- **iStent (Glaukos).** Implanted in the trabecular meshwork, the stent allows aqueous humor to flow from the anterior chamber into Schlemm’s canal (FDA approved in 2012).



Glaukos recently received approval for a pivotal U.S. trial of the iStent SA system (consisting of 2 stents in a single inserter) as a stand-alone procedure in pseudophakic patients.

- **Hydrus Microstent (Ivantis).** Described as an

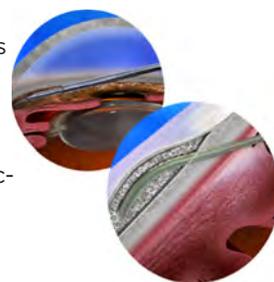
intra-canalicular scaffold, this 8-mm-long device is inserted into Schlemm’s canal to establish outflow (approved in Europe but not in the United States or Canada).

#### 2. Targeting the suprachoroidal space:

- **CyPass Micro-Stent (Alcon).** This device, implanted in the supraciliary space, allows suprachoroidal aqueous outflow (FDA approved in 2012. [NOTE: Voluntarily withdrawn from global market, August 2018]).

#### 3. Opening a subconjunctival filtration pathway:

- **XEN 45 Gel Stent (Allergan).** This soft, collagen-derived gel device creates a new pathway for aqueous flow from the anterior chamber into an ab interno bleb in the subconjunctival space (FDA approved in 2016).



### Nonimplant MIGS

- **Trabectome (NeoMedix).** Electrocautery, irrigation, and aspiration are used to selectively ablate the trabecular meshwork and the inner wall of Schlemm’s canal to allow aqueous free access to the canal and its collector channels (FDA approved in 2004).

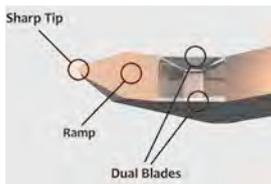
- **Kahook Dual Blade (New World Medical).** This relatively inexpensive single-use disposable handpiece employs 2 parallel blades to remove a strip of trabecular meshwork to im-

Results of the entire cohort showed that IOP was reduced from 16.5 mm Hg preoperatively to 12.9 mm Hg, and the mean number of medications decreased from 2.3 to 0.9.

**Reducing medication burden.** “At 12 months, 94% of all eyes achieved their predefined treatment goal of reduced IOP and/or medications,” Dr. Gallardo noted. Among patients who had medically controlled glaucoma entering cataract surgery plus stent implantation, 69% were able to completely eliminate their need for medications. Of this latter group, 55% had been on 3 or more medications preoperatively, he said.

“The earlier we use MIGS, the less we need to rely on medications,” Dr. Gallardo said.

He noted several benefits from reducing a patient’s medication burden: increased compliance, lower monthly costs (generic drugs are skyrocketing in price), and less exposure to the preservative benzalkonium chloride, which has been associated with ocular surface disease and damage to endothelial cells in the trabecular columns.

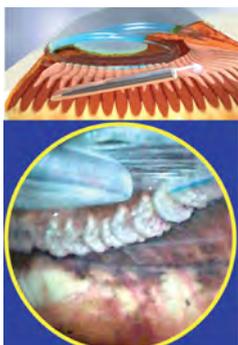


prove outflow, without need for an expensive electrocautery or irrigation/aspiration system.

• **Gonioscopy-assisted transluminal trabeculotomy.** GATT is

a minimally invasive ab interno circumferential trabeculotomy (see Fig. 1, next page) that is performed through two 1.0-mm corneal incisions and employs either a microcatheter, 5-0 Prolene suture, or TRAB 360 handpiece (Sight Sciences). After cannulation, the entire trabecular meshwork is unroofed.

• **Ab interno canaloplasty (ABiC).** The procedure, performed through a single self-sealing clear corneal incision, involves 360-degree viscodilation of the canal using either the iTrack microcatheter (Ellex) or the VISCO360 (Sight Sciences) handpiece and an ophthalmic viscoelastic device inserter.



• **Endoscopic cyclophotocoagulation (ECP).** An endoscopic probe is inserted via a corneal or pars plana incision to ablate a selected portion of the ciliary epithelium under direct endoscopic visualization. This process decreases aqueous production.

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**ABiC: Impact on Practice**

Dr. Gallardo also performs ab interno canaloplasty (ABiC), or transluminal viscodilation, which aims to improve outflow by dilating Schlemm’s canal 360 degrees through a small corneal incision, using a microcatheter and viscoelastic.

**Pearls for ABiC.** He makes the temporal clear corneal wound directly across from the nasal angle with side-port incisions at a 90-degree angle. He recommends avoiding the limbal vessels as much as possible, as surface bleeding can stain the viscoelastic used as a coupling agent for the gonioscope and obstruct the view of the drainage angle.

Dr. Gallardo uses the iTrack catheter, which, he said, “provides tactile feedback on the patency or health of the canal during circumnavigation, while the illuminated tip allows me to track the catheter’s movement, providing me assurance that I am actually in the canal and not in the suprachoroidal space.”

**What about moderate to severe glaucoma?**

Dr. Gallardo said that the advent of MIGS has had an enormous impact on his practice, not only in his treatment of patients with mild glaucoma but also in those with moderate to severe glaucoma.

“Whether [they are] performed as a standalone procedure or as an adjunct to cataract surgery, I have found these microinvasive procedures very effective at meeting my patients’ needs,” he said. “In patients requiring further reduction in IOP, I try a MIGS procedure or a combination of MIGS procedures before filtering, in most but not all circumstances.” He added, “I was doing 8 to 10 filters a week, and now I perform 1 ab externo filtration every 4 to 6 weeks.”

**GATT: A New Twist on Trabeculotomy**

While ABiC is a minimally invasive approach to canaloplasty, gonioscopy-assisted transluminal trabeculotomy (GATT) is a minimally invasive modification of standard trabeculotomy.

“When I was a medical student, I felt that trabs and tubes seemed really harmful to the eye, and I kept questioning why we were doing what we were doing,” said glaucoma specialist Davinder S. Grover, MD, MPH, of the Glaucoma Associates of Texas in Dallas.

“I started practice right around the time the iStent was being investigated,” Dr. Grover added. “My partners and I were primary investigators on the CyPass microstent, Hydrus, and XEN gel stent. Additionally, Dr. Ronald L. Fellman and I were developing techniques of our own (ab interno bleb revision and ab interno Ex-PRESS shunt removal), and all this research converged to provide a productive environment for our own innovations.”

**Development of GATT.** Drs. Grover and Fellman

(along with their colleagues Drs. David Godfrey and Oluwatosin Smith) developed the GATT procedure, an ab interno circumferential trabeculotomy that is performed through 2 corneal incisions, 1 mm each. A small goniotomy is created, and a microcatheter or 5-0 Prolene suture is used to cannulate 360 degrees of Schlemm's canal and then unroof the entire trabecular meshwork (Fig. 1).

Dr. Grover said a major advantage of this procedure is that the entire drainage system is accessed, rather than just a small portion. In addition, it spares conjunctival tissues from incision and scarring, allowing better outcomes if traditional glaucoma surgery is required later.

**Findings from 2 studies.** In the first study, "we looked back at our 2-year data on 10 patients (14 eyes) under 30 years old with a dysgenic anterior segment angle and uncontrolled primary congenital glaucoma or juvenile open-angle glaucoma who underwent GATT," Dr. Grover said. "They experienced a mean decrease in IOP from 27.3 to 14.8 mm Hg and a mean decrease in meds from 2.6 to 0.86.<sup>4</sup>

"Moreover, when we evaluated GATT outcomes in 198 patients with POAG and secondary open-angle glaucoma (SOAG), either isolated or combined with cataract surgery, we found very encouraging results that were similar to if not better than previously published data on ab externo circumferential trabeculotomy," Dr. Grover said.

The patients in this study with POAG had an average IOP decrease of 9.2 mm Hg (a mean reduction of 37.3%) at 24 months, with an average decrease of 1.43 glaucoma medications.

At that same time point, the SOAG patients had an average decrease in IOP of 14.1 mm Hg (a mean reduction of 49.8%) on an average of 2.0 fewer medications.<sup>5</sup>

**Learning from failure.** While Dr. Grover was pleased with the results, he gained greater insight from the treatment failures. In the POAG group, there was a correlation between mean devia-

tion (MD) in visual field defect parameters and outcomes: Patients with a worse MD had a higher chance of treatment failure in the first 3 months.

"This is suggestive of the health of the eye's inherent drainage system," Dr. Grover said. "Since it is difficult to visualize the collector channels and episcleral vasculature, we searched for other indicators that would serve as a proxy to determine the patency of the outflow system."

**The wave as an indicator.** In seeking such a proxy, Drs. Fellman and Grover drew on their experience with an earlier MIGS, Trabectome. During that type of surgery, they had observed a nasal perilimbal and/or episcleral vessel wave of fluid adjacent to the trabeculotomy site. "We believe this fluid wave, which we named an episcleral venous fluid wave (EVFW), signifies intraoperative structural patency of the conventional outflow system and is a sign that the collector system is at least anatomically functional."<sup>6</sup>

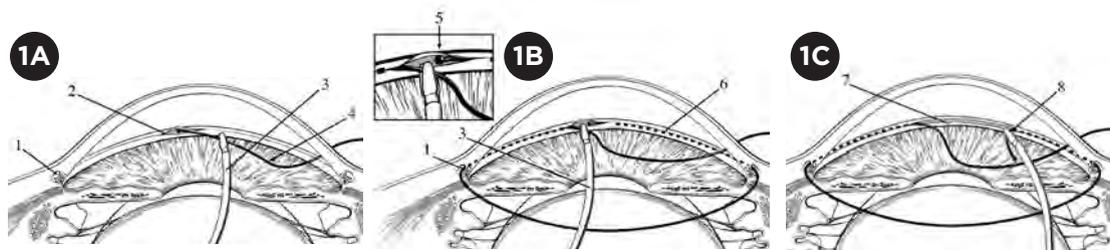
Dr. Grover said the presence or absence of this EVFW could be a prognostic indicator for success after a Trabectome surgery. In a study of 68 eyes of 49 patients with glaucoma who underwent phaco plus Trabectome or Trabectome alone, the eyes with a poorly defined EVFW had a higher likelihood of further glaucoma surgery.<sup>7</sup>

He uses the EVFW as a prognostic sign for GATT as well. "When I perform a GATT and I see an EVFW, I am very optimistic about that surgery."

### Combined MIGS Procedures

One of the hot topics at the American Glaucoma Society's 2017 annual meeting was combining MIGS procedures. Won I. Kim, MD, a glaucoma specialist with Walter Reed National Military Medical Center in Bethesda, Maryland,\* gave a presentation suggesting that multiple MIGS procedures can be successfully combined without significant additional risk.

Dr. Kim said, "Because of their relatively modest efficacy, MIGS procedures have traditionally been



**KEY STEPS IN GATT.** (1A) Initial cannulation of Schlemm's canal. (1B) The microcatheter (or suture) has been passed 360 degrees around the canal. (1C) The distal tip of the catheter/suture has been retrieved and is being externalized, creating the circumferential trabeculotomy. KEY: 1, Schlemm's

canal (SC); 2, initial goniotomy site; 3, microsurgical forceps; 4, either the microcatheter or suture; 5, distal end of the catheter/suture after it has been passed around SC; 6, path of the catheter/suture within SC; 7, trabecular shelf created by this procedure; 8, trabeculotomy resulting from GATT.

limited to mild to moderate disease; but perhaps combined MIGS procedures, with their potentially improved efficacy, can be extended to include those with severe disease.”

**Mix-and-match MIGS.** Dr. Kim has been mixing and matching MIGS procedures, based on specific patients’ needs. One of these combinations is ab interno trabeculectomy plus ABiC.

“My approach was removing a section of trabecular meshwork with the Trabectome or Kahook Dual Blade and then viscodilating the rest of Schlemm’s canal 360 degrees with the iTrack,” Dr. Kim said (Fig. 2). “This could take advantage of the different mechanisms of both sectoral trabecular meshwork removal and canaloplasty while simultaneously addressing their weaknesses,” such as the limited sectoral aspect of Trabectome and the residual trabecular meshwork resistance after canaloplasty.

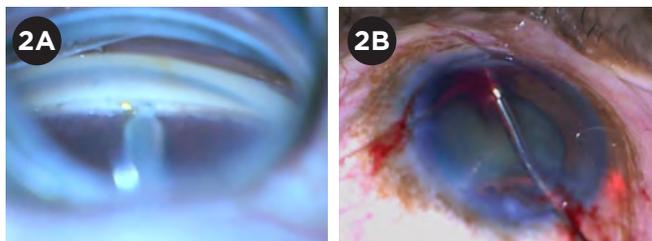
He has also successfully used several other multi-technique approaches. These include ABiC combined with micropulse transscleral cyclophotocoagulation (TSCPC; Fig. 3), trabecular meshwork bypass (using either iStent, GATT, or Trabectome) combined with endoscopic cyclophotocoagulation (ECP; Fig. 4), and CyPass supraciliary stent combined with trabecular meshwork bypass (using iStent or Kahook Dual Blade; Fig. 5).

He said that in his experience, all of these techniques have shown the ability to lower IOP into the low-teens range, reduce medication burden, maintain an excellent safety profile, and allow for rapid visual recovery.

**Multi-MIGS plus phaco.** Dr. Berdahl is also an advocate of combined MIGS. He compared the outcomes of combined microbypass stent implantation, cataract extraction, and ECP to those obtained with just the microbypass stent and concomitant cataract surgery in patients with OAG.<sup>8</sup>

He found that patients who underwent the combined approach experienced a mean IOP reduction of 7.14 mm Hg compared with 4.48 mm Hg in the control patients who did not have ECP. He found that the combination procedure was also effective in patients with severe OAG.

“The combined approach makes sense,” Dr. Berdahl said. “We are trying to avoid the morbidity of more aggressive glaucoma surgeries. The question then becomes whether the efficacy is good enough. My approach is safety first and efficacy second. I will try the MIGS first.”



**TRABECTOME + ABiC.** (2A) Trabectome is used to remove a sector of trabecular meshwork. (2B) ABiC is performed through the Trabectome’s ablation zone.

### MIGS Caveats

Steven L. Mansberger, MD, MPH, of the Devers Eye Institute in Portland, Oregon, has closely watched the advent of MIGS. He expressed concerns in the areas of efficacy and costs.

“As a glaucoma specialist, I am always interested in finding new ways of lowering pressures safely and effectively, and I applaud the investigators in this space,” Dr. Mansberger noted.

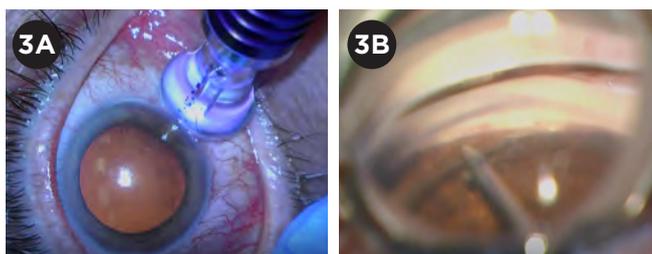
“That being said,” he added, “MIGS may be useful for some patients, but traditional surgeries are required by the vast majority of surgical glaucoma patients, and it is imperative that we continue to learn the ins and outs of trabs and tubes in our glaucoma fellowships.”

**Efficacy concerns.** Dr. Mansberger pointed out that some MIGS such as the iStent make only a millimeter of difference in IOP, and “we do not understand the characteristics of patients who most benefit from MIGS above and beyond cataract surgery alone.”

Dr. Mansberger recounted a number of earlier implant devices that had failed, including several limbal and suprachoroidal stents in the 1950s and 1960s, and a XEN-like implant in the 1980s.<sup>9</sup>

“We have new modifications such as mitomycin C [e.g., with XEN implants],” he added. “But time will tell if these new MIGS will be more effective or if history will repeat itself.”

**Cost factors.** The downside of many of the MIGS surgeries is their cost, Dr. Mansberger pointed out. MIGS such as iStent, XEN, and Trabectome can add up to \$4,000 to the cost of cataract surgery alone when factoring in surgeon charges, device costs,



**TSCPC + ABiC.** (3A) After micropulse TSCPC is completed, (3B) ABiC is performed.



**GATT + ECP.** (4) TRAB 360 handpiece is used to perform GATT, which is followed by ECP.

drops or who have severe glaucoma, we do a traditional procedure, and we only need to operate one time to treat the problem. That is preferable to multiple surgeries,” he said.

“Down the road, MIGS will be considered based on cost, IOP response, and visual field outcomes,” said Dr. Mansberger. “Through the efforts of these MIGS pioneers, we will learn more about how to better treat glaucoma. We don’t have the perfect MIGS yet, but in the end, we will get there.”

anesthesia costs, and surgical center fees. “We need to look at changing the cost-benefit ratio in terms of costs,” Dr. Mansberger said.

On the other hand, he noted that the GATT procedure is one of the most cost-effective MIGS—it can be done using a \$5 suture. “And Dr. Grover has shown good results 2 to 3 years out, making this the approach to watch,” Dr. Mansberger said.

**Multiple surgeries?** He also has concerns about patients who may need subsequent surgeries if a MIGS procedure does not effectively lower IOP.

“In most patients we see who can’t use their

### The Next Phase: Sustainability

Dr. Ahmed expressed a similar view regarding future developments. He said that while it has been greatly satisfying to be involved in the early innovation process and see a large number of MIGS procedures “go mainstream,” he had not fully anticipated the need for research on their cost-effectiveness and appropriate utilization.

**Reimbursement challenges.** “We are currently recognizing and building the right studies to look at quality-of-life issues, helping payers in the United States and Canada understand why MIGS should be funded a certain amount,” Dr. Ahmed

## A Comprehensive Ophthalmologist’s Perspective on MIGS

Do MIGS have a place in the comprehensive ophthalmologist’s armamentarium? Absolutely, according to Jeffrey Whitman, MD, a comprehensive ophthalmologist at the Key-Whitman Eye Center in Dallas.

“In our cataract patients with mild to moderate glaucoma, if we can get them off even one of their eyedrops by utilizing a MIGS approach, then we should offer this alternative,” Dr. Whitman said. “One eyedrop may not seem like much, but over the course of a lifetime, that adds up to significant savings and greatly impacts the quality of life.”

**iStent, CyPass, and beyond.** Dr. Whitman has been inserting iStents for the past 3 years and, within the last year, has begun using the CyPass. “In my early experience, I find the CyPass somewhat easier to insert, and I am obtaining much lower pressures than I could have imagined,” he said.

He believes that the field will continue to advance, perhaps with combinations of MIGS or the addition of medications to stents for more potent treatment. (Glaukos and other companies are investigating these possibilities.)

**MIGS myths limiting usage.** Dr. Whitman observed that misconceptions about the effectiveness of MIGS procedures, the learning curve, and the time MIGS adds to cataract surgery are preventing many comprehensive ophthalmologists from adopting this approach.

“I encourage comprehensive ophthalmologists not to give up on MIGS but rather to reach out to other ophthalmologists and learn better techniques,” Dr. Whitman said. “In terms of time, it makes an efficient cataract surgery take up to 50% longer, but I believe the benefits to the patient are well worth it.”

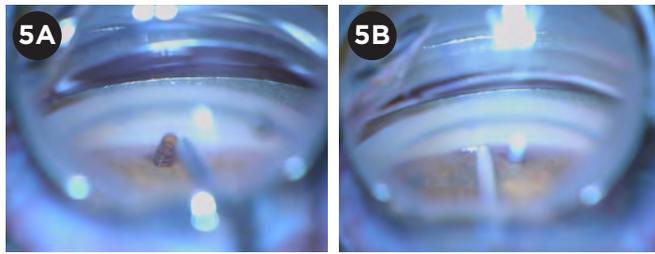
**Getting comfortable with MIGS.** He added that getting accustomed to using a gonioscopic lens to view the angle and keeping the magnification at 9× (higher magnification results in less depth of field) will help comprehensive ophthalmologists become more comfortable with learning to do MIGS.

“My real take-home message to my colleagues is to get on the bandwagon with MIGS,” Dr. Whitman said. “It doesn’t add much time to cataract surgery, and it provides great benefit to your patient.”

said. “We are looking at recovery, number of postsurgical visits, return to vision, and refractive changes—metrics that are of concern to entities funding these procedures.”

Dr. Berdahl also pointed to reimbursement as one of the biggest challenges to widespread MIGS adoption. “MIGS is one of the only really impressive innovations in glaucoma in the last few decades. It will be tremendously sad if it withers on the vine,” he said, for lack of reimbursement and resources to support innovation.

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**CYPASS + ISTENT.** (5A) CyPass is placed in the supraciliary space. (5B) iStent-L is placed, followed by an iStent-R facing in the opposite direction (not shown). The 2 iStents and a CyPass allow aqueous outflow through multiple pathways.

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**MORE ONLINE.** See this article at [aao.org/eyenet](http://aao.org/eyenet) for video resources, additional images, and more.

## Meet the Experts



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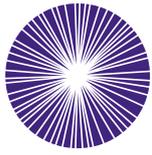
**Won I. Kim, MD** Glaucoma specialist with Walter Reed National Military Medical Center and professor of surgery at Uniformed Services University of the Health Sciences (USUHS), both in Bethesda, Md.\* *Relevant financial disclosures:* None.

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**Jeffrey Whitman, MD** President and chief surgeon of the Key-Whitman Eye Center in Dallas. *Relevant financial disclosures:* Glaukos: C,L; Ivantis: C.

**See disclosure key, page 5. For full disclosures, view this article at [aao.org/eyenet](http://aao.org/eyenet).**

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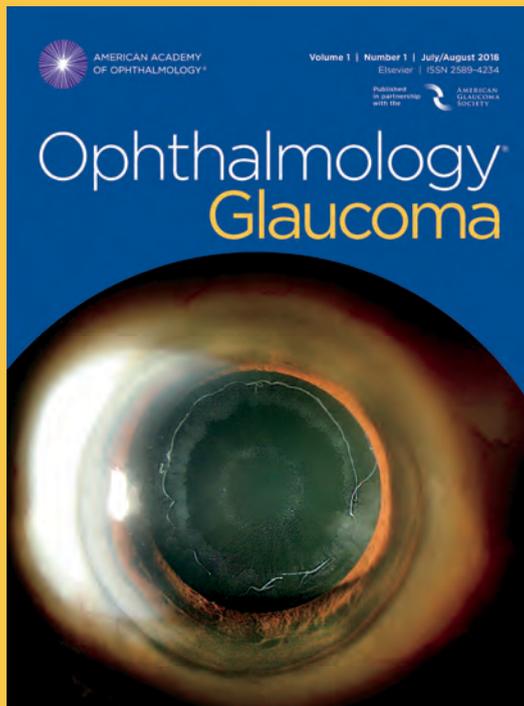


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### BRIEF SUMMARY

Consult the Full Prescribing Information for complete product information.

### INDICATIONS AND USAGE

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

### DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

### WARNINGS AND PRECAUTIONS

#### 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 previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

#### Use with Contact Lenses

RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

### ADVERSE REACTIONS

#### Clinical Trials Experience

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

#### Corneal Verticillata

Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intraocular administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

#### Animal Data

Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses  $\geq 0.3$  mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on  $C_{max}$ ). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on  $C_{max}$ ).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on  $C_{max}$ ). Malformations were observed at  $\geq 3$  mg/kg/day (1330-fold the plasma exposure at the RHOD, based on  $C_{max}$ ), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on  $C_{max}$ ).

#### Lactation

There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

#### Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years 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

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.



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For more information, go to [www.RHOPRESSA.com](http://www.RHOPRESSA.com) or call 1-855-AerieRx (1-855-237-4379).

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