2020 IN REVIEW

Glaucoma 360

PUBLISHED AS A SUPPLEMENT TO
Ophthalmology Times®

GLAUCOMA
RESEARCH FOUNDATION

ONCE-DAILY
rocklatan®
(netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%

Superior efficacy. Optimal simplicity.[1,2]

Once-daily Rocklatan® significantly lowers IOP in patients with open-angle glaucoma or ocular hypertension—superior to latanoprost and netarsudil at every measured timepoint in phase 3 clinical trials.[1,2]

The first and only once-daily fixed-dose combination of prostaglandin + ROCK inhibitor

IOP

Nearly 60% of Rocklatan® patients achieved a target pressure of 16 mmHg or less[2]

The majority of ocular adverse events were mild and tolerable, with minimal systemic adverse events[1,3]

QD

Once-daily dosing relieves treatment burden and may improve adherence and treatment outcomes[1,4]

IOP: intraocular pressure; ROCK: rho kinase

Visit Rocklatan.com to learn more about this innovative drop for elevated IOP

IMPORTANT SAFETY INFORMATION

Contraindications
None.

Warnings and Precautions
- Pigmentation changes
- Eyelash changes
- Intraocular inflammation
- Macular edema
- Herpetic keratitis
- Bacterial keratitis
- Contact lens wear

Adverse reactions
Rocklatan®: The most common ocular adverse reaction is conjunctival hyperemia (59%). Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Netarsudil 0.02%: Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%: Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reaction.

Please see brief summary on the adjacent page.

For full Prescribing Information, please visit Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is approved 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. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

References:
1. Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% Prescribing Information, Aerie Pharmaceuticals, Inc., Irvine, Calif. 2019. **2.** Asrani S, McKee H, Scott B, et al. Pooled phase 3 efficacy analysis of a once-daily fixed-dose combination of netarsudil 0.02% and latanoprost 0.005% in ocular hypertension and open-angle glaucoma. Presented at the 13th Biennial Meeting of the European Glaucoma Society, March 2018. **3.** Data on file. Aerie Pharmaceuticals, LLC. **4.** Prum B Jr, Rosenberg L, Gedde S, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern guidelines. *Ophthalmology.* 2016;123(1):P41-P111.

aerie Pharmaceuticals, Inc.

Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

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If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Pigmentation
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Beyond 5 years the effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with Rocklatan® can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
Rocklatan® contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
Rocklatan® contains latanoprost which should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because it may exacerbate inflammation...

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Rocklatan® 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.

Herpetic Keratitis
Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

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.

Use with Contact Lenses
Contact lenses should be removed prior to the administration of Rocklatan® and may be reinserted 15 minutes after 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 trials of another drug and may not reflect the rates observed in clinical practice.

Rocklatan®
The most common ocular adverse reaction observed in controlled clinical studies with Rocklatan® was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Other adverse reactions that have been reported with the individual components and not listed above include:

Netarsudil 0.02%
Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%
Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

DRUG INTERACTIONS
Although specific drug interaction studies have not been conducted with Rocklatan®, in vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost ophthalmic solution 0.005%. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on netarsudil ophthalmic solution use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous 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 ≥0.3 mg/kg/day (126-fold the plasma exposure at the 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 ≥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}).

For latanoprost, in 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

Lactation
There are no data on the presence of netarsudil or latanoprost 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. It is also not known whether latanoprost or its metabolites are excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rocklatan® and any potential adverse effects on the breastfed child from netarsudil and latanoprost.

Pediatric Use
Safety and effectiveness 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
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.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

For additional information, refer to the full prescribing information at www.Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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GLAUCOMA 360

The quest for a cure

GRF annual series of events unite research, industry, philanthropy

Glaucoma Research Foundation (GRF) gathered in early February—perhaps one of the last ophthalmic conferences to convene in-person before the impact of the coronavirus pandemic—for the 2020 edition of its Glaucoma 360 meeting. Held at a new venue, the Grand Hyatt San Francisco at Union Square, the triad event intertwined celebration, innovation, and education in its efforts to eradicate glaucoma.

The three-day event included the Annual Gala, GRF's primary fundraising event and the celebratory portion of activities, followed by the ninth annual New Horizons Forum, the innovation segment of the annual meeting that featured panelists and speakers from more than 60 companies and institutions. The program concluded with two sessions at the Glaucoma Symposia offering continuing education credits for ophthalmologists and optometrists.

Following a reception, the Annual Gala treated more than 380 attendees to a live auction and dinner, as well as a matching gift opportunity as part of the Fund-A-Scientist Initiative.

"Glaucoma 360 is the GRF's signature event highlighting innovations in glaucoma therapy and helping to accelerate patient access to the latest and most effective diagnostic tools and treatment options," said Thomas Brunner, president and CEO of the foundation.

The Annual Gala bestowed accolades on innovators in research, medicine, and industry, as well as philanthropists.

The conference was co-founded by Adrienne L. Graves, PhD, a board member of GRF and an independent director on the boards of many ophthalmic companies, and Andrew G. Iwach, MD, chairman of the GRF board of directors, and executive director, Glaucoma Center of San Francisco. The pair envisioned bringing together research, medicine, industry, and philanthropy to focus on glaucoma. Preparations are under way for the 2021 GRF meeting, which will take place as a virtual event.

This special supplement from *Ophthalmology Times*®—strategic media partner with the Glaucoma 360 meeting—highlights some of the many presentations. ◗

For exclusive *Ophthalmology Times*® Video Interviews from Glaucoma 360, go to **OphthalmologyTimes.com/Conferences/Glaucoma-360**

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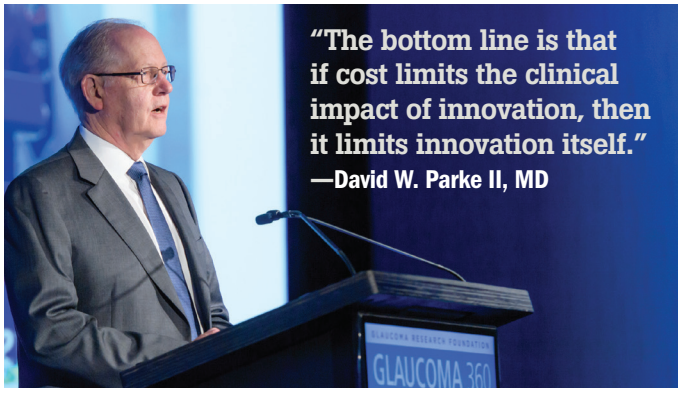
Fostering innovation in the face of costs, policy issues

Innovation is major force in cost increases, not increased productivity

Patients and physicians alike clearly benefit from innovations in treatment. However, the conundrum is clear: how can innovation continue to be fostered in the face of health-policy issues and economics?



"This is the reality in which we live," said David W. Parke II, MD, CEO of the American Academy of Ophthalmology (AAO), as he delivered the Drs Henry and Frederick Sutro Memorial Lecture, "When Cost and Innovation Collide in Ophthalmology."

The importance of this in today's political environment cannot be overemphasized. Health care is the No. 1 or No. 2 issue for voters and more specifically, the cost of health care. It is probably the issue in Washington, DC, on which both parties are united, Parke said.

But this is where the picture becomes muddied. Concerns about cost do not involve 1 drug or device but affect everything in health care and every practice in ophthalmology.

"The bottom line is that if cost limits the clinical impact of innovation, then it limits innovation itself," Parke said.

The goals from a health care policy perspective are cost reduction for patients and society as well as improved access to quality care. But is this possible to achieve when considering the exponential increases in the average annual costs of care per patient over the past 40 years and the one-third increase in co-payments in the United States in about 3 years where the country's health care costs far exceed those of every other country?

A domino effect is apparent: increased costs have real societal effects; treatments cost more than patients, employers, and taxpayers can afford; medication adherence decreases; and nonadherence costs billions of dollars in avoidable health care costs. Innovation has been shown in multiple economic studies to be the major force in cost increases, not increased productivity on the part of the physicians and their increased revenue.

Medicare seems to be a maze of inequality in drug pricing and valuing of services. A prime example was a 15% decrease in cataract surgery payment because of the effect of endocyclophotocoagulation on the re-evaluation of the entire family of codes.

"This is an example of the intersection of innovation and cost," he said.

New pricing approaches are being looked at with an eye toward value-based pricing, in which the pricing is linked to the value achieved by a new drug. Indication-specific pricing is another consideration; that is, when a drug or device is indicated for the treatment of 2 diseases and achieves better results in 1 disease, the pricing may change accordingly.

AAO's role

Recently, the AAO IRIS Registry has been providing insights into real-world evidence from more than 75 million patient records from more than 18,000 physicians—with data from over 5 million patients with glaucoma and those with suspected glaucoma. The data provide the basis for forming policy and analyzing decisions.

"It is our role as experts in the professional community and industry to help to try to reconcile and move the models forward," he said.

"Some market regulation will always be required, and we will be moving to some form of value-based practice, and the perfect value-based pricing has yet to be described," Parke added. "We are all going to benefit from more granular data on processes and outcomes so that we can get to a sustainable equilibrium that rewards innovation and ultimately moves our profession forward."

Glaucoma devices: Now and in the future

Leaders discuss IOP monitoring, drug delivery, data collection

Diagnostic and interventional technologies are improving continuously.

Both ends of the spectrum are equally important for patients with glaucoma, with an eye toward individualized treatment, according to Thomas Samuelson, MD, adjunct professor of ophthalmology, University of Minnesota, Minneapolis, and in private practice at Minnesota Eye Consultants, and Dale Heuer, MD, retired professor and chair of ophthalmology, Medical College of Wisconsin, Milwaukee.

Both were co-moderators of a panel comprised of industry leaders.

Much of the discussion focused on intraocular pressure (IOP) monitoring, drug delivery technologies, and collection of glaucoma data.

Here are some of the highlights.

Diagnostic approaches and data collection

One such advance that is creating excitement is in interventional glaucoma, which is "the marrying of IOP-monitoring devices to drug-delivery technologies," explained Ramin Valian, leader of an interventional glaucoma team, Allergan.

This approach will allow the identification of the patient and provide the appropriate treatment of the patient.

"IOP monitoring is an evolving technology that can advance glaucoma management to the next frontier," Valian said.

Jane Rady, MS, MBA, senior vice president of corporate strategy and business development, Glaukos, is looking to futuristic monitoring in the form of goggle-based artificial intelligence (AI) systems for monitoring visual fields that has potential for use at home and in practice.

"This would provide visual data in a far more physician- and patient-friendly fashion," she said.

Downsides of this may be patient education to ensure correct use of the technology and cost, added Monika Fischer, MSc, senior market manager for visual fields, Haag-Streit Diagnostics.

Another monitoring technology is fluorescence lifetime imaging (Heidelberg Engineering).

Kfir Azoulay, MBA, corporate head of strategy, Heidelberg Engineering, commented that this is an exciting innovation that allows measurement of the lifetime of fluorophores. The technology provides accurate and very early metabolic imaging at stages that are currently invisible to clinicians ophthalmoscopically or with existing technologies.

"With this technology, a molecular change translates to a new pattern that can be detected on the retina upon which AI can be applied," he said.

He also looks to the contributions of faster optical coherence tomography (OCT) engines, acquisition, and higher resolution in glaucoma diagnosis.

Bringing monitoring technologies to nontraditional settings that connect back to the physician lately has become more and more of a consideration.

Angelo Rago, head of global ophthal-

Continues on page 8

WORKING TO EMPOWER A NEW ERA OF

PROACTIVE GLAUCOMA SURGERY

> We might see a day in which the subjective portion of surgery is minimal and **we have more objective ways of lowering IOP.**
>
> **— Dr. Arsham Sheybani**

Santen is partnering with glaucoma surgeons to improve glaucoma surgical outcomes.

Santen

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AdvancingGlaucomaSurgery.com

Continued from page 6

mic diagnostics, Carl Zeiss Meditec, believes that this will provide a more holistic view of how a patient is progressing in glaucoma management.

He also noted that on the surgical side, pre- and postoperative data can be used to ensure the best possible outcomes.

For example, information garnered from the placement of a toric intraocular lens using the Callisto system (Carl Zeiss Meditec) later could be extended to minimally invasive glaucoma surgeries.

Fischer also agrees with the usefulness of connecting the data. "We will see huge changes by having everything in one place in an easy-to-read format," she said.

One step further would be the use of AI to flow that data in the right direction to better determine individual patient needs. AI, she noted, also can help in screening to identify potential patients with undiagnosed glaucoma.

In line with this, Azoulay noted that early, accurate identification of patients who may be severely impacted by glaucoma for their lifetime is inherently difficult to achieve because currently no such technology exists.

He echoed the sentiment that the true solution may lie in the conglomeration of data from various devices and displaying that data intelligently to clinicians to facilitate individualized decision making for patients along with the application of deep learning algorithms.

"Expecting one modality to do that now is not available in the foreseeable future," he said.

Rago sees a possible home use in the future for OCT in predicting visual field progression in patients with mild to moderate glaucoma.

"We may see monitoring devices using known technologies come to the home that were not thought of previously," he commented.

Drug delivery systems

The increasing availability of injectable drug delivery systems ultimately may replace drop therapy.

> *The longer the safety duration of the therapy, the more likely [it] is that a product will become a first-line therapy.*
>
> *—Jane Rady, MS, MBA*

However, this would require adjustments in business models and patient perspectives to adopt such a different technology in a glaucoma practice; in other words, integrating injectable systems into practice may be more challenging that it appears, Valian added.

In line with this, Samuelson noted, a trend that will be helpful to the adoption of drug-delivery systems is the benefit to the ocular surface, because there is less toxicity than with topical therapies.

Rady highlighted the potential safety durations of the various injectable delivery systems as key to their successful replacement of topical glaucoma treatment.

"The longer the safety duration of the therapy, the more likely [it] is that a product will become a first-line therapy," she commented.

The duration of activity and the clinical burden on practitioners may or may not be the same as seen in the retina community. Combination therapies also will come into play by providing convenience and efficacy for patients and physicians, she added.

Paul Halen, MS, global head of glaucoma and retina, Alcon Vision LLC, also sees movement toward an investment in injectable-delivery systems that will help deal with ocular surface and patient compliance issues.

"The introduction of combination therapies down the road makes sense," he said.

Santen is looking toward a number of drug-delivery options, noted Victor Chan, MS, MBA, head of US marketing and sales for surgical devices, Santen. The company has prioritized the development of preservative-free drops to maintain the health of the ocular surface, Chan added. ◗

GLAUCOMA 360 *online exclusives*

Funding new technologies for glaucoma treatment
With an eye toward innovation, panelists highlight how money is driving research for new therapies, devices
OphthalmologyTimes.com/new-tech-glaucoma-treatment

Glaucoma devices provide impressive IOP-lowering results
Representatives from industry describe their company's new devices, both invasive and non-invasive for treating glaucoma
OphthalmologyTimes.com/glaucoma-devices-lower-iop

Glaucoma drug-delivery devices enter new frontier
Industry applies creative approaches to help increase patient adherence
OphthalmologyTimes.com/glaucoma-drug-delivery-new-frontier

Developing a new therapy: Where do we go from here?

Researchers must weigh emotional, financial, and reputational considerations

Great inventions start with an idea, but only a small fraction move past that phase through increasingly complicated, work-intensive developmental stages.

Leaders in the field guided investigators through the route their ideas must take to reach fruition. Malik Kahook, MD, professor of ophthalmology, University of Colorado, and Adrienne Graves, PhD, cofounder and cochair of Glaucoma 360, moderated this discussion.

Developing an idea

Considerations when attempting to "grow" an idea into a viable product are the risks involved—emotional, financial, and reputational. "These factors seem theoretical until they become real, as people are judging if your approach is sound," said John Berdahl, MD, who is in private practice at Vance Thompson Vision, Sioux Falls, South Dakota.

The next step is determining if the idea is good (ie, interesting and important) and can satisfy a marketable need. This stage must be coupled with a high level of motivation to pursue that idea and accomplish the level of work needed to bring it to realization. Finding mentors, performing proof-of-concept science, and being honest with all involved individuals about whether the idea will take off are also mandatory steps.

Importantly, the idea must be legally protected with a patent. Entrepreneurs must protect a space to prevent others from developing something similar. Berdahl also offered a practical tip: develop the intellectual property before starting the company and then license the property to the company for a royalty. Physicians must also learn about how venture deals are structured, executing a business, and staying focused.

Forge pathways through the FDA and reimbursements. Berdahl advised engaging early with the FDA (which provides useful information about achieving approval) and payers to determine what can be reimbursed. Team building is the final and perhaps most vulnerable step to assemble a group of people who are dedicated to making the idea a reality.

The prototype

"The next step after developing a medical prototype is raising capital," said Reza Zadno, PhD, CEO of Glaukos. This is easier said than done for novice entrepreneurs. Raising capital also presents questions about who benefits from the product, the patient with better outcomes, the provider with shorter surgical times and better economics, or the payers?

"The most exciting projects for potential investors are those that satisfy everyone—generally high-risk, high-benefit projects," Zando said. "However, they are also more difficult. A clear path is needed because the patients, provider, payer, and the costs of goods are generally unclear."

The parties involved evoke myriad questions. For regulators: the FDA history with similar products, regulatory pathway, and is the product paid for by the patient or reimbursed? Have investors lost money with similar products? Are providers interested in new technology?

In some cases, a prototype is not always necessary.

Experience is key to selling the project—with an experienced founder who can define a clear pathway and risk for investors and with experienced capitalists who will ultimately invest in the project.

The funding

Every step in the process of developing a new treatment involves establishing and ensuring continuous funding, according to Eugene de Juan Jr, MD, vice chairman of ForSight Labs.

The key to keeping venture capitalists interested in a project is by reducing risk, he noted.

"Entrepreneurs must design, think, [create a] prototype, and test continuously to show that whatever they have is working," he said.

To ensure the money flow, developers must ask if the product solves a clinical need.

"Human experience is what drives the needle, rather than in vitro and animal models," de Juan emphasized.

Another consideration is the form. He continued, "Is it attractive? Do patients, doctors, and payers like it?"

Some thoughts for ophthalmologists to live by: Costs increase immensely with decreasing risk as the clinical programs progress. The risks of not progressing through the stage of development increase with each step; failing early can be absorbed by large, not small, companies.

There is a 50% chance of a drug getting through a phase 2 trial. Overall, the success rate from a drug to a clinical approved outcome is about 1 in 100.

The key for not failing late is not to start if failure is in the cards.

The regulations

The Center for Drug Evaluation and Research ensures that safe and effective products are available for the American public. "Our goal is to try to approve products that are safe and efficacious," said Wiley Chambers, MD, deputy director of the Division of Transplant and Ophthalmology Products in the Center for Drug Evaluation and Research of the FDA.

When a product is involved in the approval process, Chambers advises applicants not to do something that they believe the FDA wants them to do when the company and the FDA do not think it is necessary.

The product being tested must have a vehicle that is an acceptable control.

The noninferiority margin is based on multiple previous drug trials. The 95% confidence interval that shows the test product produces the same result as the other products most of the time within 1 mm Hg indicates that within that margin, the drugs are the same, he explained.

"Human experience is what drives the needle, rather than in vitro and animal models."
—Eugene de Juan Jr, MD

In the United States, the generic solutions of timolol, bimatoprost, latanoprost, and travoprost have the same active and inactive ingredients in the same concentrations and these can be used in clinical trials.

The FDA requires comparisons of the peak and trough times of the drug tested and the control, that the measurements are done 2 weeks after treatment onset to be certain of the drug's effect, and measurements are performed at 12 weeks because drugs that work then continue to be efficacious after that time. The FDA also wants drugs to be studied bilaterally as long as the eyes are within 5 mm Hg.

"There are reasons behind everything the FDA asks for," he said. "If you don't know the reason, please ask."

Tips from the trenches

If considering a start-up, Thomas A. Mitro, president and chief operating officer of Aerie Pharmaceuticals Inc., advised hiring the best, most experienced people, who are not necessarily the most affordable, to lead the company through start-up turmoil.

In line with that, he also advised that they be paid well and not in stock options, before another company scoops them up.

Virtual start-up companies (and departments within those companies)—although very attractive—are difficult to build and establish the company culture and repertoire among employees scattered across the United States and globally.

To combat the negative aspects of having a company with multiple sites worldwide, Aerie Pharmaceuticals brings all employees together at 1 location for an annual meeting. The company also encourages immediate decision making by employees.

"Quick start-ups are encouraged and in like manner, fail as quickly as possible. Long exits waste time and money," Mitro said.

He advised companies not to fall prey to failures by other companies in the industry that are attempting similar start-ups.

Finally, Mitro advised building relationships, not enemies; other companies should be considered competitors who are treated with respect. ◗

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Glaucoma medications: Getting down to basics

New therapies on the horizon offer options for slowing progression

Exciting new pharmaceuticals are in the pipeline. Here is a taste of information presented at the Glaucoma 360 meeting in a session co-moderated by Leslie Jones, MD, department chair and director of glaucoma services at Howard University Hospital, and Ruth Williams, MD, a glaucoma specialist at the Wheaton Eye Institute.

Because recent murine and human genetic studies have identified the role of the angiopoietin/Tie2 pathway in development and maintenance of Schlemm's canal and IOP control, Aerpio Pharmaceuticals has hypothesized that restoring Tie2 activation using topical razuprotafib (AKB-9778) could restore Schlemm's canal integrity, improve outflow facility, and decrease IOP and perhaps open-angle glaucoma progression.

The drug works by inhibiting vascular endothelial protein tyrosine phosphatase, the most downstream regulator of the Tie2 pathway, resulting in restored Tie2 activation.

"We believe that targeting VE-PTP [vascular endothelial protein tyrosine phosphatase] is the most effective approach pharmacologically to restore Tie2 activation," said Kevin Peters, MD, chief scientific officer and vice president of research and development, Aerpio Pharmaceuticals.

Peters explained that the same function is seen in humans. All preclinical and clinical testing of the drug thus far has resulted in "significant" decreases in IOP with good tolerability, he explained. The drug also lowered IOP in combination with standard-of-care prostaglandins. AKB-9778 is the first-in-class Tie2 activator for targeting primary open-angle glaucoma via the conventional outflow pathway and has capability for use as an adjuvant therapy, as a potential drug to repair the outflow pathway, and to possibly stop glaucoma progression.

Direct targeting of the vessels and tone would have an exponential effect on the retinal perfusion, the key driver in glaucoma.—Sevgi Gurkan, MD, MS, founder and chief executive officer, Perfuse Therapeutics

Brian Murphy, MD, chief executive officer, Emerald Bioscience, reported on work being done with synthetic cannabanoid-based targeted therapeutics, specifically cannabanoid derivatives. A prodrug of tetrahydrocannabinol (THC), THC-valine-hemisuccinate, is under study to lower IOP and provide neuroprotection to the optic nerve; this research is based on the recognition that the eye has the highest density of cannabinoid receptors in the body (except for the brain) on ocular structures that regulate IOP.

Murphy emphasized the possible potential of this drug in Asia, which has a predominance of normotensive glaucoma. A drug that is directly neuroprotective would be important in that market, he explained.

Investigations thus far have shown that nanoparticles of THC-valine-hemisuccinate can penetrate both the anterior and posterior ocular compartments.

"TCH-valine-hemisuccinate achieved a substantial drop in IOP compared to timolol and pilocarpine," he explained but pointed out that the drug has a short half-life.

The company reported the results

of a rabbit model that showed a high degree of bioavailability, with the drug delivered to various eye tissues. The topical preparations resulted in significant reduction of IOP in that model.

Mannin Research is developing 2 novel treatments to target the angiopoietin Tie2 mechanism of action to repair the normal outflow channel in the eye; 1 is a small molecule with once-daily administration of a topical drop (MAN-01) and the other is an injectable protein agonist of Tie2 to treat primary open-angle glaucoma, noted Doris Qamar, MBA, director of business development.

Qamar announced a partnership between Mannin Research and Pendant Biosciences with the goal of developing a novel extended-release formulation to deliver the MAN-01 small-molecule biologic to treat glaucoma. This nontoxic product releases without bursts and consistently over an extended period. "This is the future of glaucoma treatment," she said.

Qamar noted that Heather Sheardown, BEng, PhD, is currently developing a product to be used with the small molecule to significantly improve the bioavailability of topical drugs with the goals of reducing dosing, administration frequency, and unintended systemic exposure.

Mannin Research is also developing a tool to help diagnose glaucoma severity and progression. The technology will require an aqueous humor tap in the clinic, a first-in-class diagnostic test. The biomarker is in clinical trials. The companion diagnostic, she explained, will help physicians identify and stratify segments of the glaucoma population regarding disease severity and progression and those who will likely benefit from the therapeutic.

Nicox Ophthalmics' glaucoma products are based on a nitric oxide (NO) research platform that leverages the central role of NO in maintaining the IOP homeostasis in the anterior segment, said Tomas Navratil, PhD, executive vice president, head of research and development.

In addition to the development and commercialization of latanoprostene bunod ophthalmic solution 0.024% (Vyzulta) most of the company's efforts are now focused on 2 clinical-stage products that resulted from this research. NCX 470 is a second-generation NO-donating bimatoprost analog, which entered its first phase 3 trial in the second quarter of 2020. The second product, NCX 4251, may be a potential treatment for patients with acute blepharitis and dry eye. NCX 4251 is expected to enter a larger phase 2B clinical trial.

In a phase 2 28-day study, NCX 470 showed "statistical superiority to latanoprost in the mean diurnal IOP and statistical superiority in time-matched IOP at 8 and 10 AM and 4 PM compared with latanoprost. This is important, as we use this methodology for the primary efficacy outcome measure in phase 3 studies," Navratil said. IOP decreased in a range of 7.6 to 9.8 mm Hg, which he described as the most robust IOP lowering by a drop seen in a clinical trial.

The dose response in the trial was exciting in that there was linearly increasing IOP lowering with each subsequent drug dose; hyperemia peaked at the mid dose, plateaued, and did not increase with the high dose (0.065%). The safety profile was good.

Navratil also described that 2 products are being researched for glaucoma: NO-donating PDE5 inhibitors that target increased primary outflow from the anterior segment that are envisioned as first-line therapy, adjunctive therapy, or in a fixed-dose combination with a prostaglandin analog.

Perfuse Therapeutics is developing its products based on the idea that IOP reduction alone is insufficient in glaucoma and that blood flow in the eye is mediated by perfusion pressure and vessel response to the ever-changing perfusion pressure. Direct targeting of the vessels and tone would have an exponential effect on the retinal perfusion, the key driver in glaucoma, explained Sevgi Gurkan, MD, MS, founder and CEO, Perfuse Therapeutics.

The company is pursuing endothelin-1 antagonists, the primary regulators of vascular tone that are upregulated in many ocular diseases, via intravitreal delivery every 6 months to target the vascular. Preclinical results showed induction of ischemia in multiple species that was reversed to baseline with the trial drug. Investigators also studied a preclinical glaucoma model with sustained elevated IOP leading to ganglion cell death; the structure and function of the cells were shown to be preserved by the experimental drug. ◗

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Next frontier in glaucoma: Non-IOP-lowering treatments
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OphthalmologyTimes.com/glaucoma-non-iop-lower-treatment

Diagnostics: Innovative ways of looking at glaucoma
Learn what industry panelists have to share about how novel products may increase the chance of early diagnosis.
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Thinking outside the box for alternative glaucoma therapies

Nontraditional treatments may offer some hope for patients

Most patients with glaucoma respond to some degree to medical, laser, or surgical therapies designed to lower intraocular pressure (IOP). However, there are some patients who do not respond to those treatments, or who prefer additional routes to lower IOP or protect their optic nerves.

Although the only proven therapies are those that lower IOP and include medications, lasers, and surgeries, patients frequently inquire about other options. Among these are marijuana, ginkgo biloba, memantine, acupuncture, meditation, blood pressure modification, and certain supplements as possible therapeutic candidates, explained Shan C. Lin, MD, codirector of research at the Glaucoma Center of San Francisco, California.

MARIJUANA, which is legal for use in California, does lower IOP, but the duration of the effect is very short—about 3 hours—which would require the patient to use the drug almost continuously.

Potential downsides include concomitant lowering of the ocular perfusion pressure (by lowering the blood pressure) and addiction. The American Academy of Ophthalmology does not recommend marijuana as a primary treatment for glaucoma, Lin noted.

"There are better treatments to lower eye pressure, and it is not something that I recommend to my patients," Lin continued.

Calcium influx into the retinal ganglion cells starts the apoptotic cascade; memantine starts early in the cascade to prevent cell damage and death.—Shan C. Lin, MD

GINKGO was described by Lin as a "relatively interesting agent" for treating glaucoma and other diseases. It is an herbal supplement obtained from the leaves of the ginkgo biloba tree and has been used in Chinese medicine for 5000 years. The compounds in the herb include flavonoids, lactones, and cyanidins, all antioxidants.

"While it has not been completely established exactly how these molecules work, they may be helpful in the treatment of Alzheimer disease, stroke, and possibly glaucoma," he said.

In addition to antioxidant activity, ginkgo also preserves the mitochondria, inhibits apoptosis, and possibly increases blood flow.

In a study supporting the use of ginkgo, patients with glaucoma who had a significantly affected pretreatment mean deviation were treated with ginkgo for 4 weeks.[1]

Investigators observed improved visual fields with a substantial decrease in the amount of mean deviation. The results of a retrospective study of ginkgo for normal tension glaucoma found that the herb may stop progression of the disease.[2]

However, as many other studies do not support the herb's positive effects, the jury is still out on the matter. A significant downside is the risk of bleeding in elderly patients, according to Lin.

MEMANTINE seemed to be a promising option at one point and was studied in a large clinical trial for 5 years.

However, neither of the doses that were given were superior to placebo in preventing progression.

According to Lin, memantine works to prevent apoptosis by blocking the calcium channels in the retinal ganglion cells.

"Calcium influx into the retinal ganglion cells starts the apoptotic cascade; memantine starts early in the cascade to prevent cell damage and death," Lin explained.

Memantine is approved in the United States and Europe to treat dementia, but it can cause some neurologic side effects.

It is the hope of ophthalmologists

that memantine would be the first neuroprotective drug never came to fruition, but Lin remains optimistic that such a drug will be developed in the not-too-distant future.

ACUPUNCTURE has been attempted to treat glaucoma, but specialists have seen no overall effects regarding lowering of IOP, visual fields, or nerve scans in a recent University of California, Los Angeles study.[3] In fact, there have been slight increases in the IOP after the acupuncture sessions.

The blood pressure was lower in the non–eye-related treatment group; however, lower blood pressure for patients with glaucoma may be harmful to their optic nerve perfusion.

MEDITATION in patients with glaucoma who were randomized to this activity was found to lower IOP by about 4 mm Hg compared with a control group in a study by an Indian group.[4] Although positive effects were seen in IOP and specific chemical mediators in the body, a drawback is that patients are reluctant to undertake meditation, Lin noted.

PERFUSION PRESSURE, in other words, the difference between blood pressure and IOP, is also a factor for consideration when treating glaucoma. Interestingly, Lin pointed out, lower blood pressure is detrimental for patients with glaucoma.

"This is the new paradigm," he said, and cited the results of the Barbados Eye Study, in which lower blood pressure was associated with lower ocular perfusion pressure, as well as the Early Manifest Glaucoma Trial (NCT00000132), which found that glaucoma progression was associated with lower ocular perfusion pressure.[5,6]

MEDITATION
TAKE HOME POINTS

- **Lower eye pressure**
- **Lower levels of stress/toxic mediators**
- **Higher levels of supportive mediators**
- **Better quality-of-life measures**

Lin said he asks his patients about the status of their blood pressure and often coordinates his treatment with primary care doctors if there is pathologically low blood pressure.

Another impactful finding is that taking blood pressure medications at night, as many patients do, results in lower stroke and heart disease risk, but that is less than beneficial for the perfusion pressure as blood pressure is typically lower at night already.

Patients with physiologically low blood pressure may be advised to increase their salt intake, although this is controversial.

Other available supplements that patients can consider to possibly counteract progressive glaucoma are blackcurrant, Mirtogenol (a combination of bilberry and pine bark extracts), palmitoyl ethanolamide, and omega 3 fatty acids. Small studies have shown that they may lower IOP, increase ocular blood flow, or be neuroprotective.

Generally, the go-to treatments for glaucoma remain drops, laser, and surgeries.

"However, for patients whose glaucoma is progressing, these other agents, such as supplements and meditation, may have potential value," Lin concluded. ◗

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Assessing the angle: Getting back to basics
Sunita Radhakrishnan, MD, discusses options for treating patients with glaucoma.
OphthalmologyTimes.com/assessing-angle-glaucoma-basics

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Ruth D. Williams, MD, says for many physicians, "moral injury" may be the issue.
OphthalmologyTimes.com/beat-burnout-camaraderie

OCTA: The jury is still out
Robert L. Stamper, MD, notes diagnostic, monitoring advances may need fine-tuning.
OphthalmologyTimes.com/octa-jury-still-out

AI in medicine: The good, the bad, and the scary

Physicians will have host of tools to predict, detect, identify disease

Artificial intelligence (AI) is a hot topic today, but as with all new technologies, it has a long way to go.

A trend in medicine that is pushing the rise of AI is a doctor shortage in the United States, Europe, and China that is intensifying with the aging of the population and the need for more cost-effective treatment, according to Terri-Diann Pickering, MD, clinical instructor at the Glaucoma Center of San Francisco.

AI already has many applications in medicine: Microsoft uses AI to diagnose cervical cancer faster in India, and AI has been found to be as good as physicians for diagnosing skin cancer and better than radiologists for detecting certain breast cancers.

So, this market is growing rapidly from $2.1 billion to an estimated $36.1 billion by 2025, Pickering noted.

Four medical specialties are driving the surge in medical AI: dermatology, radiology, ophthalmology, and pathology. In some cases, AI performs better than doctors, which raises the concern about whether robots will be replacing the doctors.

"Is AI going to create good jobs, make our lives easier, or be the killer of jobs?" Pickering asked.

In the financial sector, AI is superseding well-paying Wall Street jobs, she pointed out.

"Currently, the New York Stock Exchange is devoid of humans and runs primarily by AI. And 6.14 million people working in finance and insurance are expected to lose their jobs not because they are being replaced by the machines but because they are not trained to work with algorithms," Pickering said.

AI in Ophthalmology

The first autonomous AI device in ophthalmology is the IDx-DR (IDs Technologies), which is capable of making a screening decision without a doctor and refers patients to doctors. The company worked with the FDA for 8 years to fine-tune the product. The device was studied in 900 patients at 10 primary-care offices before it received FDA approval in 2018. The IDx-DR is now being used in primary-care offices and in grocery stores. The company has purchased liability insurance in the event of injuries.

Pickering noted that AI may also be able to predict treatment outcomes and analyze a single optical coherence tomography scan to predict which patients might benefit from antivascular endothelial growth factor treatment.

"This is a step forward in precision medicine. This would save health care and patient and doctor time," she said.

There is also an Augmented Reality contact lens (Mojo Vision). This technology places micro-displays inside the eye on the retina. The company hopes to help patients with low vision.

Something else in the pipeline is robot-assisted surgery, the Steady Hand developed at John Hopkins. It eliminates tremors, is 10 times more precise than the human hand, and there is less potential to touch the retina.

However, the downsides are that the device is fairly slow and there is less degrees of motion. The Steady Hand has been approved for retinal surgery in Europe.

The Intraoperative Robotic Inter-

ventional Surgical System from the University of California, Los Angeles, has the goal of developing a fully automated cataract surgery robot and an assistant vitreoretinal surgery robot. "This is intended to help, not replace, the surgeon," Pickering explained.

For glaucoma, nothing is yet approved, but some technologies are promising, such as a study looking at forecasting future Humphrey Visual Fields using a single visual field, which can help with personalized treatment and prognosis.

An automated AI algorithm has been found to be better at diagnosing glaucoma using optical coherence tomography and visual fields in general ophthalmology practice and equal to glaucoma specialists.

Using fundus photos, an algorithm has been found to be highly accurate in identifying glaucomatous optic nerves.

In addition, AI has identified 49 previously unknown genome sites that were coupled with other known sites to develop a potential risk score and can identify people with up to 15 times increased risk of developing glaucoma at an earlier age.

We will have a host of new tools to predict glaucoma risk, diagnose glaucoma, detect progression, identify optimal treatment using precision medicine, and forecast prognosis, Pickering noted.

There is a lot of promise, but there is also the potential for risk because the systems have not been tested vigorously. Some systems have failed in healthcare centers, and a system developed in one hospital may not work in another. Software can discriminate against minorities and they can make odd predictions that have nothing to do with disease. The products have little evidence to support them and the start-ups publish press releases with no research in peer-reviewed journals.

No products have been tested in randomized clinical trials, Pickering said. "The industry needs careful oversight but the devices do not need review and approval," she said and reported that over the past decade, tens of thousands of deaths have been linked to these devices.

These products were cleared for sale because they were associated with moderate risk without testing as long as they are similar to pre-existing devices. So for right now, the take-home message seems to advocate a great deal of caution. ◗

Predicting glaucoma progression: More than meets the eye

Dale K. Heuer, MD, discussed factors that can be considered easily by physicians when evaluating their patients during the Shaffer-Hetherington-Hoskins Lecture, titled "Risk Factors for Glaucoma Progression," at the Glaucoma 360 annual meeting. "Every patient should undergo risk calculation to determine management, treatment, and follow-up," said Heuer, a retired professor and chair of ophthalmology, Medical College of Wisconsin, Milwaukee.

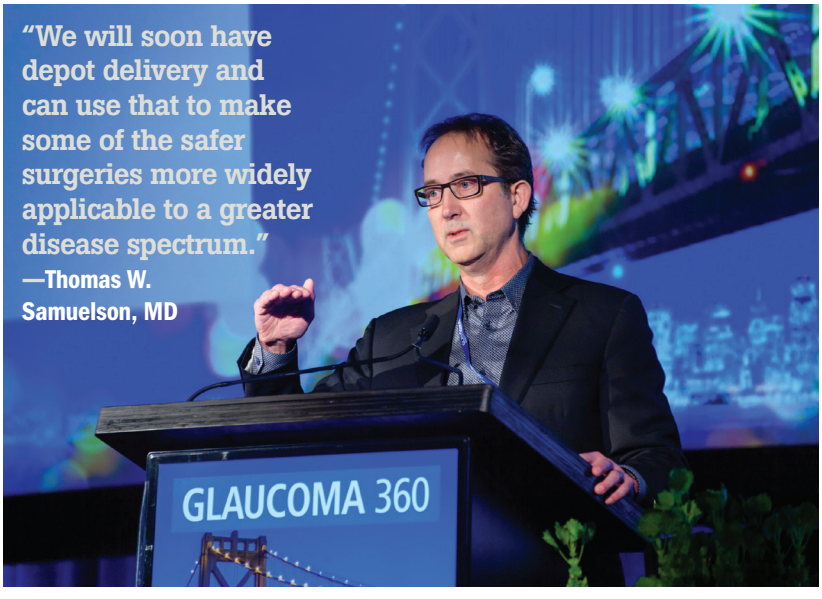
For an exclusive video interview with Heuer, go to **OphthalmologyTimes.com/glaucoma-360-risk-factors-for-glaucoma-progression**

Akorn initiative raises awareness, funds for GRF

On behalf of Akorn Pharmaceuticals, CEO Douglas S. Boothe (in collaboration with Adrienne L. Graves, PhD, who is also on the Akorn Board) presented a donation of $50,000 to Glaucoma Research Foundation (GRF) at the Annual Gala in February 2020. Akorn partnered with GRF to raise awareness about glaucoma during the observance month and to thank employees for what they do every day. The pharmaceutical company had raised enough money to fund a scientist for a full year.

Safety first: Making the best decisions in surgical glaucoma

Glaucoma interventions are akin to tightrope walking



Technology advances rapidly, even in medicine, and numerous therapies for glaucoma have been introduced over the years. But despite the advent of new and effective tools, which can be enticing for surgeons because of their very newness, limitations and weaknesses accompany them, according to Thomas W. Samuelson, MD. Therefore, balancing between safety and efficacy remains the name of the game.

"Over the decades we have overvalued surgical efficacy and significantly undervalued surgical safety," said Samuelson, who is in private practice at Minnesota Eye Consultants and is an adjunct professor of ophthalmology at the University of Minnesota in Minneapolis. He added that surgeons should do their best to avoid subjecting patients to procedures with the potential for disastrous or catastrophic outcomes unless the disease risk particularly warrants taking that chance.

Despite all the newer surgical options in glaucoma and the technical skill needed to master minimally invasive glaucoma surgery (MIGS) and traditional trabeculectomy, "wisdom and judgment in surgery are every bit as important as surgical dexterity," said Samuelson.

Upsides and realizations

Samuelson pointed out the advantageous developments for patients that have emerged over the previous decade.

"We have safer, more individualized surgery; less paternalistic approaches; more patient-centered outcomes; and realistic drug regimens that expand the scope of our safer interventions," he said. "We will soon have depot delivery and can use that to make some of the safer surgeries more widely applicable to a greater disease spectrum."

According to Samuelson, ophthalmologists are reverting to paying attention to physiologic outflow, which had all but been abandoned.

They are also moving toward a renewed recognition that they can improve the function of Schlemm's canal as evidenced by the LiGHT trial, the favorable effects of phacoemulsification on intraocular pressure (IOP), netarsudil (Rhopressa, Aerie Pharmaceuticals), nitric oxide-donating prostaglandins, and newer canal procedures. Each of these interventions, at least in part, improves physiological outflow.

Collectively, such improvements translate into reduced eyedrop therapy for older patients.

"We can also better manipulate the episcleral venous pressure, which may improve the efficacy of the canal-based surgeries, and when we have more aggressive target pressures, we bypass the canal and go through the sclera with the gel stent, trabeculectomy, or tube," Samuelson explained. "In doing so, we are bypassing the episcleral venous pressure altogether. The good news is that the pressure is lowered, and the bad news is that pressure may be lowered too much, risking hypotony."

Opting for surgery

The classic scenario is that surgery becomes the option when there is an unacceptable risk of glaucomatous progression despite medications and laser treatment. "A current strategy is for surgeons to control patients as well as possible with medications and laser until a cataract develops and then utilize the opportunity to treat both with a phaco[emulsification] plus procedure, the "plus" portion being the surgeons' favorite MIGS procedure. While there are exceptions, this has become the most common time to intervene surgically for glaucoma.

The trend seems to be to try a few medications, then proceed to the safer surgeries," Samuelson pointed out.

The 4 most common surgical choices include cataract surgery alone, cataract surgery plus canal-based surgery, transscleral surgery, or ciliary ablative surgery. In Samuelson's practice, he rarely performs only cataract surgery in a glaucoma patient, and his surgical choices have changed from performing mostly phacoemulsification trabeculectomy to a phacoemulsification plus a canal-based surgery. He also does not perform much ciliary ablative surgery until later on in the disease.

Why might surgeons prefer canal devices for phacoemulsification? Samuelson said it is important to keep 2 concepts in mind.

"[The first is that] in mild to moderate glaucoma, the outflow system is not completely dysfunctional but only mild to moderately dysfunctional. The second is what happens to the IOP during cataract surgery without altering the canal," he explained. "There is convincing, level 1 evidence that cataract surgery alone lowers IOP at least modestly for most patients with a cataract and glaucoma."

There is a great deal of evidence from 5 MIGS studies that the control arm (phacoemulsification alone) did well. But the study arm did even better, with lower IOPs and fewer medications. However, cataract surgery alone decreased the IOP in the iStent inject trial (Glaukos; NCT01444040) by 5.4 mm Hg, and by 5.3 mm Hg in the Hydrus Microstent trial (Ivantis; NCT01539239). Thus, before altering the canal in any way, on average the surgeon has improved the patient's pressure control.

This is important because performing only a cataract surgery may help avoid procedures that could be risky for patients.

"In mild to moderate disease with moderately good canal physiology, I prefer the less-is-more approach," Samuelson explained. "Also, I subscribe to Murray Johnstone's research and believe that the canal tissue is complex, dynamic, pulsatile, and 3-dimensional and not simply a hollow passive tube. Thus, I am cautious about disrupting the canal excessively."

Samuelson said he prefers "a minimalist approach for mild to moderate disease."

"That said, as we progress down the disease severity spectrum, [we should] start to favor the procedures that are more disruptive in the canal," he said. "For example, GATT [gonioscopy-assisted transluminal trabeculotomy] is a terrific choice for a patient with more significant disease risk in whom we are trying to avoid the risk of bleb-forming procedures."

For patients with mild disease, the important question to consider is which procedure is less likely to cause a longer-term fibrotic response in the canal that was working reasonably well, according to Samuelson.

"While there is definitely a role for both strategies, I believe that the stealth nature of the canal devices are more tissue friendly. [They are] less likely to cause a deleterious healing response [in the] longer term than procedures that are more ablative within the canal," he noted.

To further explain this approach, he pointed out that one can augment the pressure-lowering benefits of the phacoemulsification procedure by injecting 2 iStents (dimension, <0.5 mm) into the canal. The entire canal has a circumference of approximately 36 millimeters; thus, with this approach a surgeon leaves 98.7% of the canal undisrupted.

A prospective randomized clinical trial demonstrated the benefit of this, and it is easy to understand why the risk of longer-term harm due to fibrosis or adverse healing is negligible. Generally, Samuelson said he uses the iStent as his earliest intervention and the Hydrus Microstent at an intermediate time.

Incisional or ablative canal procedures he reserves as stand-alone options or for patients with significant disease, Samuelson noted.

"An important point for me is that we must remind ourselves that it is one thing to assume risk for ourselves, but subjecting others to risk is different," Samuelson said. "We need to constantly ask, 'What would I want for myself?' Generally, we migrate to the procedure with lower risk."

Associated with that philosophy is that while the safer surgeries lessen surgical risk, they may increase disease risk because the resultant IOPs may not be sufficiently low. Conversely, traditional surgeries are more effective, achieve lower IOPs, and reduce disease risk, but they increase the surgical risk, Samuelson concluded. ◗

Traditional glaucoma surgery in the era of MIGS procedures

Trabeculectomy may offer better results with more severe glaucoma

Trabeculectomy and tube procedures are still needed, and minimally invasive glaucoma surgery (MIGS) has a permanent niche.

Choosing the appropriate one to perform depends on the needs of the patient, not on those of the surgeons, according to Kuldev Singh, MD, MPH.

Most patients with mild to moderate, slowly progressive glaucoma do not need to undergo a trabeculectomy or tube procedure, explained Singh, a professor of ophthalmology and director of glaucoma at Stanford University in California.

"MIGS works nicely because the safety risk-to-benefit profile is very favorable for MIGS in those patients," he said.

Trabeculectomy and tubes provide more benefit for those patients with advanced glaucoma who are losing vision, and these procedures will remain beneficial for a long time.

To underscore his point, Singh cited a large population study with several thousand patients in which Bal Chauhan, MD, and colleagues evaluated how rapidly glaucoma progressed over a 7-year period.[1] They found that only about 2% to 3% of patients have rapid and catastrophic progression, he noted.

"Most of the other patients were part of a normally distributed curve around no change," Singh recounted.

However, with aging, some patients in the later decades of life begin to deteriorate, despite having intraocular pressure (IOP) in the low teens.

"With the aging of the population, we are going to see many more patients with glaucoma that is worsening. [In the case of] these patients, their parents did fine ... in [their] 70s and 80s, but [they] will have trouble with glaucoma later in life," he said.

Based on this, Singh foresees a virtual epidemic of older patients with severe glaucoma disease that requires very low IOP.

"The reason we have shied away from performing trabeculectomy and tubes in these patients is because of bleb maintenance. We must weigh the risks and benefits in individual patients to determine [whether] these procedures make sense," Singh explained.

The proof is in the pudding

Regarding trabeculectomy and tube procedures, these are excellent for lowering IOP and the results of various studies bear that out. For example, in a randomized comparison clinical trial of 5-fluorouracil and mitomycin C for a first procedure conducted in the 1990s, slightly more than 50% of patients had IOPs under 12 mm Hg after 3 years.

The Tube versus Trabeculotomy (TVT) Study (NCT00306852) of eyes that had been previously operated on showed that both procedures provided low IOPs. The more recent TVT study showed that both procedures provide low IOPs, with trabeculectomy performing slightly better with IOPs around 10 mm Hg.

In addition, according to Singh, the PreserFlo MicroShunt (InnFocus), a highly anticipated device awaiting FDA approval, did well when compared with trabeculectomy.

Both had similar results in a randomized clinical trial, but trabeculectomy also provided IOPs in the 10 mm Hg range. "From an IOP standpoint, it is hard to do better than trabeculectomy, which also might be a little better than tubes," he commented.

The results from another clinical study, conducted by Joseph Caprioli, MD, provided an interesting observation: When trabeculectomy lowers IOP a great deal, the visual fields improve.[2]

"I see this in clinical practice in patients with a 10- or 15-point improvement in the visual field index when the IOP decreases from the low teens to 5 or 6 mm Hg," Singh said.

The effect of trabeculectomy is titratable

Singh pointed out that when patients are losing vision despite IOPs in the 10- to 15-mm Hg range, surgeons may be afraid to perform trabeculectomies that might lower the IOPs into the single digits.

"Many older patients with severe glaucoma require an IOP of 6 mm Hg and not 12 mm Hg. I think we will continue to see more cases like this," he said.

This paradigm shift seems to be occurring. Singh recounted how the Aegis Study, which served as the glaucoma bible for a long time, had surgeons believing that glaucoma ceased with no further progression at an average of 12 mm Hg.

"What seemed to be happening in that study was that a subset of patients with low IOP did slightly better than those with a slightly higher IOP," he noted. "The concept of glaucoma stabilization is not great. Generally, glaucoma worsens, but in some cases there is an improvement when the IOP is lowered a great deal."

This aging of the population may be why MIGS might not replace trabeculectomies and tubes.

"When we have low IOP goals in advanced disease, we have proven success with trabeculectomies and tubes, and the former allows titration of the IOP to the desired level based on patient needs," Singh said.

I believe a patient-focused approach will emerge. The surgery is for the patient and not the surgeon.
– Kuldev Singh, MD, MPH

No one is certain whether the IOP decrease is maintained over time. "It may not last indefinitely, but in the 3- to 5-year period, I have seen patients with substantial improvement in visual function after trabeculectomy," he said.

MIGS: here to stay

Singh believes that MIGS is not a passing fad.

"[It has] added so much to our armamentarium. So many patients benefit from MIGS," he said.

The procedure started off as a microincisional surgery and evolved into a minimally invasive procedure. However, it is not the answer in every case.

Singh noted that although younger surgeons seem to prefer MIGS for a number of reasons, he advises them to keep the needs of the patient in the forefront. This is particularly so in cases where trabeculectomy, which is more labor intensive and has a lower reimbursement rate, may be a better option.

Regarding glaucoma surgery in the 2020s, Singh said ophthalmologists are seeing continuing growth of MIGS and that new and exciting devices are being developed. Many older patients with severe glaucoma need trabeculectomy.

"I believe a patient-focused approach will emerge," he concluded. "The surgery is for the patient and not the surgeon. I also believe that 6 mm Hg will become the new 12 mm Hg, and as surgeons opt out of performing trabeculectomies, those surgeons who can perform the surgeon and get the consistently lower results, I can envision a premium channel developing for this traditional surgery that may ultimately provide higher reimbursement." ◗

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Andrew G. Iwach, MD, provides a potpourri of observations and developments can help glaucoma specialists solve problems and fine-tune their practices to achieve the utmost in patient care.
OphthalmologyTimes.com/glaucoma-status-diagnostics-treatment-flux

Normal tension glaucoma: Testing diagnostic skills
James C. Tsai, MD, MBA, explains how factors other than intraocular pressure may be responsible for progressive disc cupping and visual field loss in the setting of normal eye pressures; genetic and other factors also play a role.
OphthalmologyTimes.com/normal-tension-glaucoma-testing-skills

Apps now online to aid patients with visual impairment

Technology is off to a good start, but improvements still needed

In our increasingly complicated world, accessible technology is of major importance for individuals who are visually challenged. From the perspective of patients with visual impairments, their iPhones and Android devices are their most valuable personal assistants, with both having accessibility features, according to Yvonne Ou, MD, codirector of the Glaucoma Division and vice chair for Postgraduate Education, University of California, San Francisco.

A major feature of the iPhone is VoiceOver, a screen reader that can be activated within the settings. When anything on the phone is touched, the text is read to the user. This feature works with all apps built into the phone as well as with third-party apps. Among other features, the camera in the iPhone can be used as a magnifier, a screen reader, and can help describe images.

A new technology is audio-description enabling, a feature that is made available by, for example, Netflix and other online content providers. This feature is handy when watching a movie scene in which there is no dialogue.

Another useful program is called Seeing AI. This free app was developed by a Microsoft employee who is visually impaired. "This app completes multiple tasks within 1 app instead of the user having to manipulate a large number of apps," Ou said.

Tasks include identifying currency, identifying products using a QR code, and reading documents by detecting the edges of the document; the app also uses artificial intelligence-enabled features, such as a scene feature to describe the surrounding environment, people, and facial expressions.

Be My Eyes and Aira

Be My Eyes is a free app that helps individuals who are visually challenged by connecting them with sighted volunteers via phone when they require visual assistance. When a person with visual impairment needs assistance, he or she can call and request the help of a sighted volunteer, who in turn, can then use the back camera on the phone to describe the scene to the caller. For example, Ou described having helped people read labels on canned food and set the thermostat.

In cases in which more privacy is needed, such as with legal or medical documents, one of Ou's patients recommended an app named Aira (pronounced ira). When using Aira, the person wears a pair of glasses, and a phone connects him or her to an agent to help with a desired task.

The Aira app was invaluable to aid a runner with retinitis pigmentosa in completing the Boston Marathon without a guide, Ou noted. The runner was connected to a remote agent who described the course as he ran.

Numerous challenges exist and accessibility is a huge issue for patients. Sighted individuals can contribute to better accessibility for individuals with visual impairment by providing a description of the scene in their Instagram posts, for example.

"Ophthalmologists can help their visually challenged and blind patients with their local communities," Ou concluded. "Representatives from the Lighthouse for the Blind, for example, can help patients with the various available technologies." ◗

…and the winner of the 2020 Glaucoma 360 "Perfect Pitch" is Thurein Htoo, MS, MBA, for his presentation on episcleral venous pressure (EVP) treatment. Htoo is CEO and cofounder of Qlaris Bio Inc.

Learn more about Htoo's pitch and others at **OphthalmologyTimes.com/new-tech-glaucoma-treatment**

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