Glaucoma 2018
A New Renaissance

Under Pressure®

Program Directors
Shan C Lin MD and JoAnn A Giaconi MD

In conjunction with the American Glaucoma Society

McCormick Place
Chicago, Illinois
Saturday, Oct. 27, 2018

Presented by:
The American Academy of Ophthalmology

Supported in part by an unrestricted educational grant from Aerie Pharmaceuticals, Inc.

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2018 Glaucoma Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Glaucoma Society (AGS), it is our pleasure to welcome you to Chicago and **Glaucoma 2018: A New Renaissance**.

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Program Director

Aerie Pharmaceuticals: C
AlEyegn: C
Allergan: C
Eyenova: C
Iridex: C

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Glaukos Corp.: L
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Allergan Inc.: C,S
Aurea Medical: C,O,P
Equinox: C,O
IanTech Medical: C,P
Johnson & Johnson Vision: P
New World Medical Inc.: P
Novartis, Alcon Pharmaceuticals: P
ShapeTech LLC: O,P

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Alcon Laboratories Inc.: C,S
Allergan: C,S
Ivantis: C
National Eye Institute: S
New World Medical Inc.: C
Novartis Pharmaceuticals Corp.: C,S
Ocular Therapeutix: C
Santen Inc.: C

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Glaukos Corp.: L
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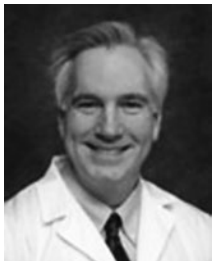
Glaukos Corp.: C,S
Gore: C
InnFocus: S
NeoMedix Corp.: L
New World Medical Inc.: S
Reliance Medical/Haag Streit: C
Transcend Medical Inc.: S



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InnFocus: C
National Eye Institute: S

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Ocular Therapeutix: C,S
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Glaucoma 2018 Contents

CME Credit

The Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement in physician practices, resulting in the best possible eye care for their patients.

2018 Glaucoma Subspecialty Day Learning Objectives

Upon completion of this activity, participants should be able to:

- Describe innovations in the diagnosis and management of glaucoma within their historical context
- Manage complex cases of glaucoma when other eye diseases are present
- Evaluate the current status of optic disc and retinal nerve fiber layer imaging and its role in diagnosing and managing glaucoma
- Demonstrate familiarity with current issues in medical and surgical therapy for glaucoma, both open-angle and angle-closure variants
- Identify and manage glaucoma surgical complications

2018 Glaucoma Subspecialty Day Target Audience

This activity has been designed to meet the educational needs of general ophthalmologists, glaucoma specialists and other ophthalmologic subspecialists, and allied health personnel who are involved in the management of glaucoma patients.

2018 Glaucoma Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

The Academy designates this live activity for a maximum of 7 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Teaching at a Live Activity

Teaching instruction courses or delivering a scientific paper or poster is not an *AMA PRA Category 1 Credit*™ activity and should not be included when calculating your total *AMA PRA Category 1 Credits*™. Presenters may claim *AMA PRA Category 1 Credits*™ through the American Medical Association. To obtain an application form please contact the AMA at www.ama-assn.org.

Scientific Integrity and Disclosure of Conflicts of Interest

The American Academy of Ophthalmology is committed to ensuring that all CME information is based on the application of research findings and the implementation of evidence-based medicine. It seeks to promote balance, objectivity, and absence of commercial bias in its content. All persons in a position to control the content of this activity must disclose any and all financial interests. The Academy has mechanisms in place to resolve all conflicts of interest prior to an educational activity being delivered to the learners.

The Academy requires all presenters to disclose on their first slide whether they have any financial interests from the past 12 months. Presenters are required to verbally disclose any financial interests that specifically pertain to their presentation.

Control of Content

The American Academy of Ophthalmology considers presenting authors, not coauthors, to be in control of the educational content. It is Academy policy and traditional scientific publishing and professional courtesy to acknowledge all people contributing to the research, regardless of CME control of the live presentation of that content. This acknowledgment is made in a similar way in other Academy CME activities. Though coauthors are acknowledged, they do not have control of the CME content, and their disclosures are not published or resolved.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the American Academy of Ophthalmology must verify your attendance at Subspecialty Day and/or AAO 2018. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the *Subspecialty Day Syllabi* exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2018 course or session room.

CME Credit Reporting

South Building Level 2.5 and Academy Resource Center

Attendees whose attendance has been verified (see above) at AAO 2018 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2018 at the CME Credit Reporting booth.

Academy Members

The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2018 credits entered at the Academy's annual meeting will be available to Academy members through the Academy's CME web page (www.aao.org/cme-central) beginning Thursday, Dec. 13.

The Academy transcript cannot list individual course attendance. It will list only the overall credits claimed for educational activities at Subspecialty Day and/or AAO 2018.

Nonmembers

The Academy provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity. To obtain a printed record of your credits, claim CME credits onsite at the CME Credit Reporting kiosks. Nonmembers choosing to claim online through the Academy's CME web page (www.aao.org/cme-central) after December 13 will have one opportunity to print a certificate.

Proof of Attendance

The following types of attendance verification are available during AAO 2018 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite registration receipt
- Instruction course and session verification

You must have obtained your proof of attendance at the CME Credit Reporting kiosks onsite, located in South, Level 2.5, and in the Academy Resource Center.

The American Glaucoma Society (AGS) Subspecialty Day Lecture

The Future of Sensors in the Diagnosis and Monitoring of Glaucoma

Saturday, Oct. 27, 2018
11:43 AM – 12:13 PM

Marlene R Moster MD

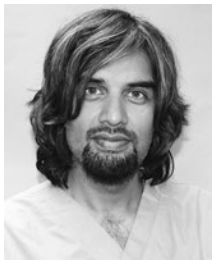
Marlene Moster MD is an attending glaucoma surgeon at Wills Eye Hospital and professor of ophthalmology at Thomas Jefferson University School of Medicine in Philadelphia. Her research interests include pharmacologic advancements in the treatment of glaucoma and surgical interventions to minimize risk and improve outcomes of glaucoma surgery, with particular interest in newer devices.

Dr. Moster has authored over 100 peer-reviewed publications and many chapters in ophthalmology textbooks, and she has edited a book on anesthesia in ophthalmology. She has been invited to give many named lectures, including the Stephen A Obstbaum MD Honored Lecture at the American Society of Cataract and Refractive Surgery's (ASCRS) Glaucoma Day and the Dickerson and Goodner lectures.

She is committed to teaching and has trained hundreds of residents and 109 clinical glaucoma fellows. She has served on the Glaucoma Clinical Committee for ASCRS and the board of the American Glaucoma Society.

Dr. Moster has been listed in *Best Doctors in America* and "Top Doctors" in the Philadelphia area for many years and has been recently awarded the Academy's Lifetime Achievement Award. She has been invited to lecture nationally and internationally on the surgical and medical treatment of glaucoma.

Faculty



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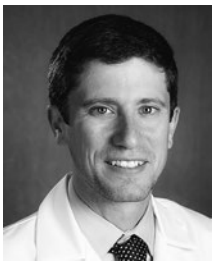

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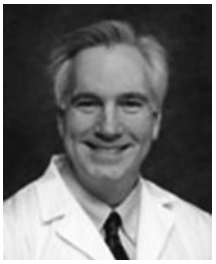

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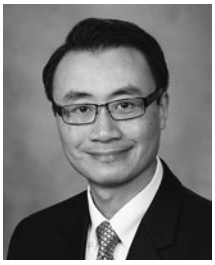

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AGS Cares

Joshua R Ehrlich MD MPH

AGS Cares is an exciting initiative of the American Glaucoma Society dedicated to providing surgical glaucoma care at no cost to qualifying uninsured patients. AGS Cares addresses a major unmet need for glaucoma care among U.S. patients with limited financial resources. We invite you to join more than 80 of your colleagues from throughout the United States as an AGS Cares surgeon and give back to your community. When you donate your time and expertise to provide surgical and postoperative care to those most in need, the American Glaucoma Society will pay for the remaining costs of patients' care through the generous, ongoing support of our corporate sponsors and other donors.

Please do not hesitate to contact me if I can provide any additional information about this exciting and worthwhile initiative of the American Glaucoma Society.

Ask a Question and Respond to Polls Live During the Meeting Using the Mobile Meeting Guide

To submit an answer to poll or ask the moderator a question during the meeting, follow the directions below.

- Access at **www.aao.org/mobile**
- Select Program, Handouts & Evals
- Filter by Meeting – Glaucoma Meeting
- Select Current Session
- Select "Interact with this session (live)" Link to open a new window
- Choose "Answer Poll" or "Ask a Question"

Glaucoma 2018: A New Renaissance

In conjunction with the American Glaucoma Society

SATURDAY, OCT. 27

7:00 AM	CONTINENTAL BREAKFAST		
8:00 AM	Welcome and Introductions	JoAnn A Giaconi MD	
8:02 AM	American Glaucoma Society Introduction	Cynthia Mattox MD FACS*	
8:04 AM	America Glaucoma Society Cares	Joshua R Ehrlich MD*	xiv
8:07 AM	Announcements	JoAnn A Giaconi MD	

Section I: New Drug Session

Moderators: Leon W Herndon Jr MD* and Kuldev Singh MD MPH*

8:09 AM	History of Glaucoma Medications	Wallace L M Alward MD*	1
8:19 AM	Nitric Oxide–Donating Drugs	Gail F Schwartz MD*	2
8:26 AM	Trabecular Meshwork–Targeted Drugs	Yvonne Ou MD*	4
8:33 AM	Alternative Drug Delivery Systems: How Close to Prime Time?	James D Brandt MD*	6
8:40 AM	What Compounds Are Up Next?	John R Samples MD*	9
8:47 AM	How Do Drug Availability and Pricing Affect the Practice of Glaucoma?	Joshua D Stein MD MS*	10
8:54 AM	Discussion		

Section II: Secondary Glaucoma—Pseudoexfoliation?

Moderators: Anna K Junk MD and Molly Walsh MD MPH*

9:09 AM	Introduction	Anna K Junk MD	
9:11 AM	Clinical Hallmarks and Natural History of Pseudoexfoliation	John Danias MD PhD	13
9:17 AM	Genetic and Environmental Background of Pseudoexfoliation	Janey Lee Wiggs MD PhD	14
9:23 AM	How Genetics Translates to Schlemm Canal Outflow: The Role of Microfibrils	Rachel W Kuchtey MD PhD*	15
9:29 AM	What Makes Pseudoexfoliation Glaucoma So Different From Other Open-Angle Glaucomas?	Robert Ritch MD FACS*	16
9:35 AM	Systemic Manifestations of Pseudoexfoliation	Louis R Pasquale MD*	18
9:41 AM	Treatment Algorithms of Pseudoexfoliation	Karen M Joos MD PhD*	19
9:47 AM	Tailored Approach to Cataract Extraction in Pseudoexfoliation	Richard K Lee MD*	21
9:53 AM	Panel Discussion: What Do I Do Differently With Patients Who Have Pseudoexfoliation?		
10:03 AM	REFRESHMENT BREAK and AAO 2018 EXHIBITS		

Section III: New Surgeries

Moderators: David G Godfrey MD* and Lama A Al-Aswad MD MPH

Virtual Moderator: Cynthia Mattox MD FACS*

10:33 AM	Introduction and Indications	David G Godfrey MD*	

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

10:35 AM	How Do I Choose the Right MIGS?	Brian A Francis MD*	22
10:41 AM	Ab Interno Filtration	Manjool M Shah MD*	25
10:47 AM	Ab Externo Microshunt	Iqbal K Ahmed MD*	26
10:53 AM	Supraciliary Stents: The CyPass Story	Michelle R Butler MD*	27
10:59 AM	TBA	Thomas W Samuelson MD*	
11:04 AM	Angle Surgery	Patrick Gooi MD*	29
11:10 AM	Devices in Canal	Thomas W Samuelson MD*	30
11:16 AM	Discussion/Case Presentations		
11:36 AM	Advocating for the Profession and Patients	Jeff S Maltzman MD	32

The American Glaucoma Society Subspecialty Day Lecture

11:41 AM	Introduction of the Lecturer	Cynthia Mattox MD FACS*	
11:43 AM	The Future of Sensors in the Diagnosis and Monitoring of Glaucoma	Marlene R Moster MD*	35
12:13 PM	Presentation of the Award	Cynthia Mattox MD FACS*	
12:14 PM	LUNCH and AAO 2018 EXHIBITS		

Section IV: New Diagnostics

Moderators: Annette L Giangiacomo MD and Robert N Weinreb MD*

1:26 PM	Introduction	Annette L Giangiacomo MD	
1:28 PM	Triggerfish Update	Arthur J Sit MD*	36
1:35 PM	Home Monitoring of Visual Fields	Robert T Chang MD*	37
1:42 PM	How to Use Macular Ganglion Cell Complex Assessment in Your Glaucoma Patients	Kouros Nouri-Mahdavi MD*	38
1:49 PM	What Is the Role of OCT Angiography in Assessing Glaucoma?	David Huang MD PhD*	40
1:56 PM	Home Monitoring of IOP	Sharon F Freedman MD	41
2:03 PM	Discussion		

Section V: Angle Closure—Empirical vs. Evidence-Based Clinical Decision Making

Moderators: Vikas Chopra MD*and Tin Aung FRCS PhD*

2:13 PM	Old vs. New: Gonioscopy vs. Anterior Segment OCT for Narrow Angles and Angle Closure	Sunita Radhakrishnan MD*	42
2:20 PM	Assessing the Need for Laser Peripheral Iridotomy in Patients With Asymptomatic Narrow Angles	Hady Saheb MD MPH*	43
2:27 PM	Utility of Laser Peripheral Iridoplasty in Patients With Narrow Angles Despite Patent Peripheral Iridotomies	David S Friedman MD MPH PhD*	44
2:34 PM	Clear Lens Extraction in Primary Angle Closure With or Without Glaucoma	Paul J Harasymowycz MD*	45
2:41 PM	Role of Goniosynechiolysis and Trabecular Bypass Procedures for Angle-Closure Glaucoma	Constance O Okeke MD*	46
2:48 PM	Surgical Pearls for Glaucoma Surgery in Angle Closure	Steven D Vold MD*	48
2:55 PM	Discussion/Case Presentations		
3:10 PM	REFRESHMENT BREAK and AAO 2018 EXHIBITS		

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Section VI: Exciting New Research

Moderators: Albert S Khouri MD*and Harry A Quigley MD*

3:40 PM	Introduction	Albert S Khouri MD*	
3:41 PM	Virtual Reality and Glaucoma	Felipe A Medeiros MD*	49
3:48 PM	Use of Pluripotent Stem Cells in Glaucoma	Mary J Kelley PhD	50
3:55 PM	Tele-glaucoma	Albert S Khouri MD*	54
4:02 PM	Metabolic Imaging in Retinal Ganglion Cells	Jeffrey L Goldberg MD PhD*	55
4:09 PM	Artificial Intelligence and Glaucoma	Lama A Al-Aswad MD MPH	56
4:16 PM	Schlemm and Collector Channel Imaging	Alex Ansun Huang MD*	57
4:23 PM	In Vivo Imaging of Apoptosis	M Francesca Cordeiro MD*	58
4:30 PM	Discussion		

Section VII: Surgical Complications

Moderators: Malik Y Kahook MD* and Dale K Heuer MD*

4:47 PM	Introduction	Malik Y Kahook MD*	
4:48 PM	I Tore the PC and See Some Vitreous— Do I Still Do a Planned Ab Interno Angle Procedure?	Arsham Sheybani MD*	59
4:52 PM	Discussion		
4:56 PM	Managing Corneal Endothelial Complications of Suprachoroidal Implants	Nathan M Radcliffe MD*	60
5:00 PM	Discussion		
5:04 PM	How Do I Manage Ab Interno Xen Implantation With Associated Piercing of the Conjunctiva?	Matthew Ryan Schlenker MD*	61
5:08 PM	Discussion		
5:12 PM	What Goes Up, Might Not Come Down: Closing Hard to Mobilize Conjunctiva After Trab or Tube	Oluwatosin U Smith MD*	62
5:16 PM	Discussion		
5:20 PM	Managing Intraoperative and Postoperative Blood Reflux With Angle Surgery	Davinder S Grover MD*	63
5:24 PM	Discussion		
5:28 PM	Wrap-up	Dale K Heuer MD*	
5:31 PM	Closing Remarks	JoAnn A Giaconi MD	

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

History of Glaucoma Medications

Wallace L M Alward MD

Table 1. A Timeline of Medications Used to Treat Glaucoma

Year	Drug Class	Route	Generic Name	Trade Name
1877	Cholinergic agonists[a]	Topical	pilocarpine	
1897	Crystalline alkaloids	Systemic	strychnine	
1904	Osmotic agents[a]	Systemic	hypertonic saline	
1948	Adrenergic antagonists	Systemic	dibenamine	
1954	Carbonic anhydrase inhibitors[a]	Systemic	acetazolamide	Diamox
1955	Adrenergic agonists	Topical	epinephrine	Glaucon
1978	β-adrenergic inhibitors[a]	Topical	timolol	Timoptic
1987	α-adrenergic agonists[a]	Topical	apraclonidine	Iopidine
1995	Carbonic anhydrase inhibitors[a]	Topical	dorzolamide	Trusopt
1995	Adrenergic agonist prodrug	Topical	dipivifren	Propine
1996	Prostaglandin analogs[a]	Topical	latanoprost	Xalatan
2017	Rho kinase inhibitors[a]	Topical	netarsudil	Rhopressa

Note: The table lists only the first drugs in each class.

[a] Still available in the United States.

Selected Readings

1. De Schweinitz GE. Concerning non-surgical measures for the reduction of increased intraocular tension. In: Nance WO, Peck WH. *Glaucoma: A Symposium*. Chicago: Chicago Medical Book Co.; 1914:61-100.
2. Chandler PA. Progress in the treatment of glaucoma in my lifetime. *Surv Ophthalmol*. 1977; 21(5):412-428.
3. Realini T. A history of glaucoma pharmacology. *Optom Vis Sci*. 2011; 88:36-38.
4. Packer M, Brandt JD. Ophthalmology's botanical heritage. *Surv Ophthalmol*. 1992; 36:357-365.

Nitric Oxide–Donating Drugs

Gail F Schwartz MD

I. Nitric Oxide (NO)
   A. A gas that can diffuse across cell membranes
   B. Not *nitrous* oxide, which is commonly used for dental procedures
   C. Sodium nitroprusside and nitroglycerin are NO donors, allowing vasodilation.
   D. Synthesized endogenously by L-arginine via nitric oxide synthase (NOS)
   E. NO systemically may affect vascular tone, neurotransmission, immune cytotoxicity, and others.

II. Nitric Oxide Mechanism of Action
   A. NO signaling is endogenously involved with trabecular meshwork (TM) contraction and relaxation via second messenger cGMP.
   B. Receptors are not required; NO allows dynamic changes in the muscle cell-like trabecular cell.
   C. NO activates soluble guanylyl cyclase to produce cGMP.
   D. In animal models and human cell culture line of TM cells, cGMP stimulates smooth muscle relaxation and vasodilation, which increases outflow through the TM and Schlemm canal.
   E. Measurement of NO via markers
      1. While NO is a gas with a short half-life, the activation of the enzyme guanylyl cyclase, which makes cGMP, persists.
      2. cGMP is upregulated in response to NO and can be measured, unlike a gas, which diffuses into cells quickly.
      3. Nitrite, like cGMP, has been shown to be a marker for NO that can be measured.[1]

III. Nitric Oxide in Glaucoma
   A. The ciliary body and outflow system in normal eyes are enriched sites of NO synthesis.[2]
   B. Aqueous humor levels of NO are reduced in glaucoma patients, as determined via paracentesis of aqueous samples during cataract surgery.[1,3]
   C. NO can have paradoxical effects, both beneficial and deleterious, depending on the dose.
      1. Higher levels of NO in the aqueous can cause optic nerve damage with ganglion cell loss.[4]
      2. NO can regulate apoptosis; a theoretical benefit utilizing the NO pathway for neuroprotection is under investigation.
      3. Three forms of NOS. Endothelial NOS (NOS3) is decreased in the trabecular meshwork, Schlemm canal, and ciliary muscle in glaucoma.[5]

IV. Latanoprostene Bunod
   A. The only commercially available product is latanoprostene bunod (LBN) 0.024%.
   B. LBN is broken down by corneal esterases into latanoprost acid and butanediol mononitrate.
   C. Butanediol mononitrate breaks down into 1,4-butanediol and NO.
   D. Latanoprost increases uveoscleral outflow.
   E. NO relaxes the TM and increases conventional outflow.

V. LBN Clinical Trials
   A. Voyager
   B. Constellation
   C. Lunar
   D. Apollo
   E. Jupiter

VI. LBN Clinical Use
   A. Dosage: once daily in the evening
   B. Preserved with BAK 0.02 mg/mL
   C. Storage
      1. Store unopened bottle in refrigerator 36°-46°F.
      2. Once opened, maintain 36°-77°F for 8 weeks.
   D. 7.5-mL bottle with 5-mL fill, turquoise cap
   E. Adverse event profile is similar to that of latanoprost with possibly more stinging on instillation due to a pH of 5.5.

VII. Other NO-Donating Drugs
   A. Nipradilol
   B. NCX 470: NO-donating bimatoprost
   C. NCX 667
   D. NO-donating dorzolamide
   E. NO-donating brinzolamide

VIII. Summary

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Trabecular Meshwork–Targeted Drugs

Yvonne Ou MD

I. Glaucomatous Damage in the Trabecular Meshwork (TM), the Diseased Outflow Site
   A. Juxtacanalicular TM as the primary site of aqueous outflow resistance
   B. Trabecular outflow is impaired due to oxidative stress and cellular debris in TM cells.

II. Mechanisms of Novel TM-Targeted Drugs
   A. Latanoprostene bunod, a nitric oxide–donating prostaglandin analogue (PGA)
      1. Increased uveoscleral outflow (PGA)
      2. Trabecular relaxation and increased trabecular outflow (NO)
   B. Netarsudil, rho kinase (ROCK) and norepinephrine transporter (NET) inhibitor
      1. Increased trabecular outflow (ROCK inhibitor)
      2. Decreased episcleral venous pressure (ROCK inhibitor)
      3. Decreased aqueous production (NET inhibitor)

III. Efficacy of New TM-Targeted Drugs
   A. First-line or adjunctive use in open-angle glaucoma and ocular hypertension
   B. Review of clinical trials

IV. Side Effects of New Outflow Drugs
   A. Latanoprostene bunod: eye pain and hyperemia
   B. Netarsudil: hyperemia, conjunctival hemorrhages, and corneal verticillata

V. Clinical Significance of Novel Mechanism of Action and Clinical Case Scenarios

VI. New TM-Targeted Drugs in the Pipeline

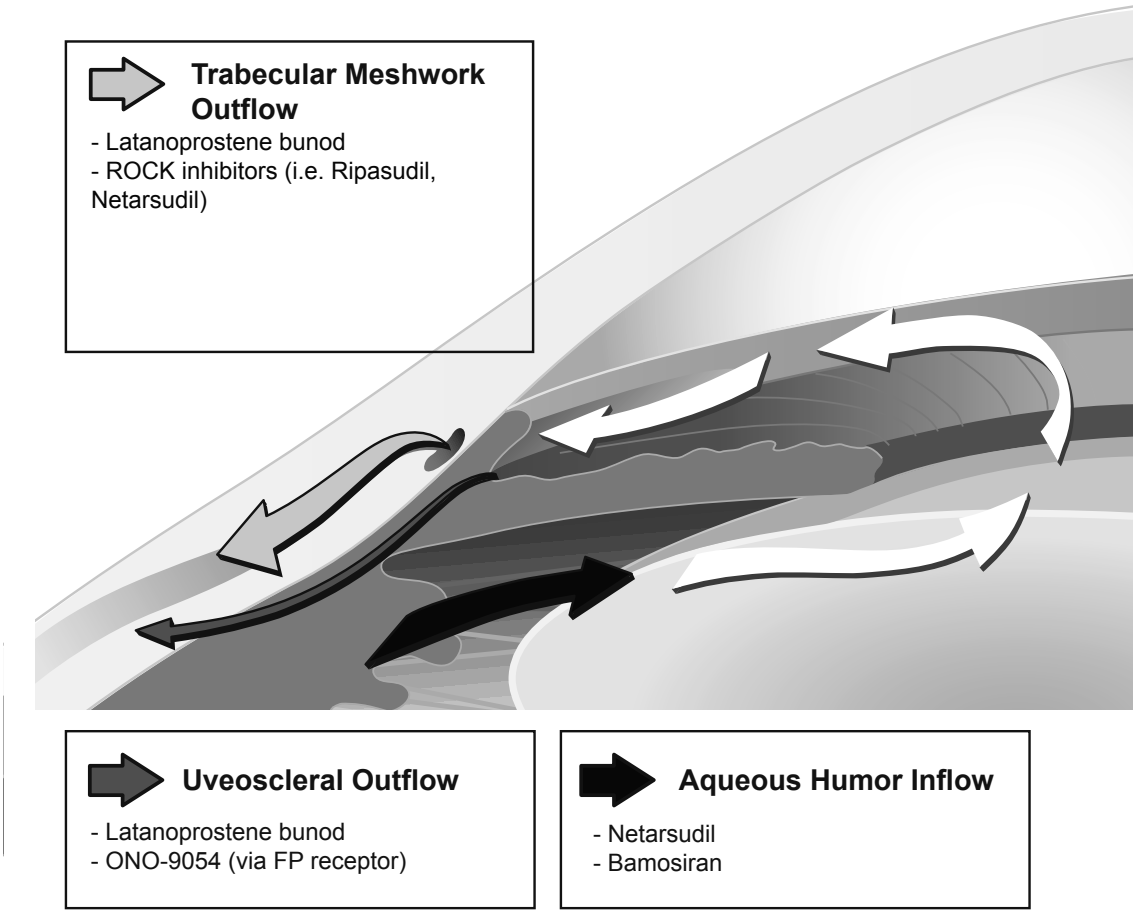

Figure 1.

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Alternative Drug Delivery Systems: How Close to Prime Time?

James D Brandt MD

The lowering of IOP remains the primary treatment goal in the management of all forms of glaucoma, whether to prevent or delay its development in individuals at risk or to stabilize neuropathy and field loss in patients with established disease. The great paradox of current glaucoma treatment is this: We have highly effective once-daily IOP-lowering medications that have been proven to reduce the likelihood of disease progression,[1] but half of our patients fail to take their eyedrops over time,[2] and we ophthalmologists are terrible at identifying the poorly adherent patient in our office.[3] This paradox is common across all of medicine—the treatment of early disease (eg, diabetes, hypertension, or hyperlipidemias) with inconvenient and sometimes costly medication results in similar 50% adherence rates, especially when a medication used to treat an asymptomatic condition causes side effects.[4]

Eyedrops as a method to deliver drugs to the eye date back centuries, and little has changed since standardized miotics were introduced in the late 1800s. The weak link in all of this is, of course, the patient, who must remember to consistently administer eyedrops to the correct eye(s) at the appropriate interval. Given competing demands on time and budget (40% of seniors in the United States took ≥ 5 prescription drugs in 2010[5]), the dexterity required to use eyedrops, and the asymptomatic nature of early glaucoma, the surprise isn't that adherence with glaucoma treatment is 50%, but that it's actually that high!

Sustained-release (SR) delivery of glaucoma medications holds great promise in addressing the challenge of poor adherence among glaucoma patients. Many novel approaches to SR glaucoma drug delivery are under development in the labs of academic researchers, biotech startups, and established pharmaceutical companies; several are in active regulatory clinical trials. A few are likely to reach FDA approval within the next 2-4 years. The purpose of this presentation is to review the SR landscape as it stands in late 2018.

The ideal SR product would deliver drug(s) to the eye with a duration of effect in alignment with patients' scheduled glaucoma surveillance visits. It would be consistently predictable, safe, tolerable, and easy to use. Though we're not there yet, we are witnessing the start of a paradigm shift in glaucoma management—it's easy to anticipate that clinicians will have a portfolio of approaches to pick from in the next decade.

Some of the SR approaches currently under development are listed in Table 1. These SR platforms can be broadly divided into *implantable* versus *external*.

While most of the SR platforms listed in Table 1 are in preclinical development in labs and animal studies, some have moved on to clinical trials (Table 2); a few are potentially approvable by the FDA within 2-4 years. Table 2 is based on publicly available documents and investor briefings published on company websites, along with a few peer-reviewed papers. Other SR platforms may be further along (or behind) than publicly acknowledged, but details of development roadmap(s) are carefully protected. A search of the clinicaltrials.gov website for "'delivery' and 'glaucoma, open-angle'" reveals about two dozen registered clinical trials in this space.

Table 1. The Sustained-Release Development Pipeline (2018)

Implantable	External
Subconjunctival	**Corneal**
Erodible drug pellets	Drug-infused contact lens
Drug-containing microspheres	
Mechanical drug reservoir (device)	
Intraocular	**Punctal**
Intravitreal	Drug-eluting punctal plugs
Suprachoroidal	
Intracameral (erodible and device)	
	Conjunctival (cul-de-sac)
	Drug-eluting ring
	Microsphere-containing gel

Table 2. The Sustained-Release Commercialization Pipeline (2018)

Product (Company)	Description	Development Stage	Targeted Duration
Bimatoprost SR (Allergan)	Biodegradable implant (anterior chamber)	Phase 3 under way	6 months
iDose (Glaukos)	Nondegradable implant (anterior chamber)	Phase 1 / 2	6-12 months
Bimatoprost Ring (Allergan)	Peri-ocular ring (conjunctival cul-de-sac)	Phase 2 complete, Phase 3 planned	6 months
OTX-TP (Ocular Therapeutix)	Punctal plug	Phase 3 under way	90 days
Evolute (Mati Therapeutics)	Punctal plug	Phase 2	90 days
Travoprost XR – ENV 515 (Envisia Therapeutics)	Biodegradable implant (anterior chamber)	Dose-ranging Phase 2	6-12 months

Among the SR platforms in or about to enter Phase 3 clinical trials, Bimatoprost SR (Allergan) is a biodegradable pellet designed to be injected into the anterior chamber; it is based on the same underlying technology as the Ozurdex dexamethasone implant. Investigators have published data from a dose-ranging Phase 1 / 2 clinical trial[6] that showed an IOP-lowering effect comparable to topically applied drug in the fellow eye out to 6 months; longer-term results were presented in a paper session at AAO 2017, but those data have not yet been published.

The iDose (Glaukos) is a nondegradable titanium implant containing a 6- to 12-month reservoir of travoprost. It is implanted into the anterior chamber angle in the operating room under gonioscopic visualization and must be surgically replaced when the reservoir is depleted. Limited efficacy data have been presented in abstract form, but no peer-reviewed papers have yet been published. Travoprost XR (Envisia) is biodegradable implant inserted into the anterior chamber. Again, limited efficacy data have been presented at meetings, but no peer-reviewed papers have been published as of June 2018.

Moving outside the eye, the Bimatoprost Ring (Allergan) device contains a 6-month reservoir of bimatoprost. The ring resides externally in the patient's cul-de-sac and releases drug into the tear film; it is not biodegradable and must therefore be replaced by the clinician every 6 months. Long-term data from Phase 1 and 2 clinical trials[7, 8] suggest efficacy similar to twice-daily timolol. Multidrug versions of the ring (eg, bimatoprost + timolol) are under development.

Punctal plug delivery of prostaglandin analogues (PGAs) is another approach under development. The amount of drug that can be loaded onto punctal plug SR platforms is constrained by the size of the device(s), so duration is likely limited to 90 days or less. Early versions of punctal plug SR platforms experienced challenges with plug retention, but the companies claim these problems have been addressed with newer designs. We have 1 published paper reporting 30-day data from a pilot study in 17 subjects.[9]

Reality Check

Despite the excitement about these new developments, a variety of therapeutic and practical issues will have to be worked out as these new platforms reach the market. The following is a list of things clinicians will need to consider as they begin to incorporate SR glaucoma treatments into their practices.

How Predictable Is the Duration of Action?

In clinical practice we assume that if a patient is consistently taking their eyedrops, the IOP-lowering efficacy of the drug is the same at 1 month as at 6 months. The same cannot be said of drug delivered by an SR platform. All platforms contain a finite amount of drug—when that reservoir is depleted, the drug effect is gone. Presumably any SR platform the FDA approves will have to deliver on its labeled duration along with a comfortable margin for those patients who fail to return on time and fall through the cracks. The "treat and extend" paradigm used by our retina colleagues to treat AMD and DME won't work in glaucoma. Even poorly compliant AMD or DME patients will usually initiate a return visit when their vision starts to drop. In contrast, glaucoma patients don't know when their IOP is rising. It seems that the emerging technologies for home tonometry and continuous IOP monitoring will be important partners in the SR paradigm shift. Get ready for patients calling your office insisting on being redosed when their IOP starts to drift upward!

What If the Patient Has a Drug-related Side Effect?

All of the SR platforms nearing commercialization deliver 1 of 3 approved PGAs. The high potency of PGAs permits loading enough drug onto a delivery platform to last many months. Cystoid macular edema (CME) is a known, uncommon but vision-threatening drug-induced side effect of PGAs, particularly in aphakia and in pseudophakic eyes with open capsules. Aphakic eyes and pseudophakic eyes with a history of complicated cataract surgery were excluded from the only published clinical trial of an injected SR platform,[6] so we do not yet know whether or not an injected PGA will behave differently in such high-risk eyes. Similar SR dexamethasone (Ozurdex) pellets have been reported to migrate into the anterior chamber in pseudophakic eyes with open capsules,[10] so it's quite plausible that the reverse will happen, delivering much higher concentrations of PGA to the vitreous cavity. Will this induce CME and require a pars plana vitrectomy to remove a wayward pellet? We won't know until this starts happening in the real world.

In contrast, external SR platforms have the safety advantage of reversibility—if a patient develops a drug-related side effect, the platform (contact lens, punctal plug, or periocular ring) can simply be removed.

What If the Patient Needs More Than 1 Drug?

During the Ocular Hypertension Treatment Study (OHTS), after just a few years of treatment half of the patients needed 2 or more medications to achieve the OHTS' modest IOP-lowering target of 20% from baseline.[11] Remember, this was in a carefully followed cohort of patients with simple ocular hypertension, not glaucoma. Most patients with real glaucoma need more than 1 drug to achieve their therapeutic target. If these patients receive a SR PGA, many will still need to take twice-daily drops to achieve sufficient pressure lowering. Continuous delivery of 1 class of glaucoma medications is better than the patient receiving none through nonadherence, but we must not overpromise our glaucoma patients a drop-free life.

Special Considerations for Injectable SR Platforms

Repeated injections for the treatment of glaucoma will represent a new paradigm shift, and there will be both workflow and safety concerns as we move into this brave new world. For example, glaucoma is usually bilateral, and each patient will typically need bilateral injections. Will you want to inject both eyes on the same day? What about patients requiring multiple injected drugs? We simply do not know how many repeated injections a cornea can take before we start to see an effect on endothelial counts.

Conclusion

Based on what we know from publicly available information, it seems reasonable to predict that the Bimatoprost SR (Allergan) and perhaps the iDose device (Glaukos) will complete Phase 3 clinical trials in the 2019/20 timeframe and file New Drug Applications with the FDA soon thereafter. Other SR platforms, both injectable and external, will follow over the ensuing several years. The early 2020s will be an exciting time for glaucoma clinicians and their patients.

Our patients clearly want alternatives to eyedrops,[12] but it is incumbent upon us to guide them in the risks and benefits of the SR platforms as they come on to the market. We must always keep in mind that glaucoma is for most patients a slowly progressive disease, and for early glaucoma, safety must be the highest priority.

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What Compounds Are Up Next?

The Near and Far Future of Glaucoma Medical Therapy . . . The Future After Presently Approved Agents

John R Samples MD

I. The Immediate Horizon
   A. Combination therapy
      1. Combination of 2 approved drugs, netarsudil (a rho kinase inhibitor) and latanoprost
         a. Trial finished approximately April by Aerie
         b. Other companies also interested in this approach because it combines a primarily uveoscleral outflow drug with a primarily trabecular meshwork outflow, thus covering all the major pathways.
      2. Addition of nitric oxide to other prostaglandins
         a. Logical addition to almost any pressure-lowering molecule if efficacious
         b. Although all prostaglandins have some effect upon the trabecular meshwork and outflow structures, adding nitric oxide adds an additional element of meshwork treatment.
            i. Termed meshwork "relaxation"
            ii. Affects extracellular matrix of the meshwork
   B. Other new agents
      1. Santen has 2 prostaglandin drugs under development: Different receptor binding profiles and similar mechanism to other prostaglandins
         a. Prostaglandins change extracellular matrix in uveoscleral outflow pathway
         b. 24-hour pressure reduction and once-a-day dosing remain major advantages of the class
      2. Adenosine class won't go further after trabecodeonsen failure.

II. The Distant Horizon
   A. Trabecular protection
      1. Alpha agonists can be optimized to release basic fibroblast growth factor.
      2. Rho kinase inhibitor class
      3. Replacement of trabecular cells (stem cells with pharmacologic enhancement)
      4. Enhancement in conjunction with minimally invasive glaucoma surgery procedures
   B. Neuroprotection
      1. Many available strategies target caspases and activation of cell death pathways
      2. Cautionary tales of the memantine failure still loom large in decisions.
      3. Drug delivery to the optic nerve remains a major challenge.
      4. Some potential therapies include:
         a. RNA interference therapy
         b. Oral rho kinase inhibitors
         c. Nutritional therapies
            i. Goji berries
            ii. Resveratrol
            iii. Many others
      5. Much work in this area is held tightly for proprietary reasons.

III. Gene Therapy

May no longer require knowledge of a precise cause to engineer a cure:

   A. Monogenetic glaucomas
   B. Multigenetic glaucomas (the majority)

IV. Cell-Based Therapies
   A. Benefits come from understanding and modifying the basic causes of glaucoma.
   B. Primary open-angle glaucoma is not a single disease; genetics proves this.
   C. Final common pathway in glaucoma may lend itself to treatment; intraocular pressure and loss of IOP maintaining homeostasis are examples of a final common pathway.

How Do Drug Availability and Pricing Affect the Practice of Glaucoma?

Joshua D Stein MD MS

I. Factors Affecting Drug Availability

A. Availability of the raw ingredients to produce certain medications

Eg, shortages of raw ingredients to produce dorzolamide and dorzolamide-timolol have been cited as a reason for the recent shortage of these products.

B. Number of pharmaceutical companies producing a given medication

The fewer companies there are producing medications, the more difficult they can be to obtain. For example, with very few companies producing medications such as pilocarpine and atropine, they can be difficult to obtain and costly to purchase.

C. Supply of medications that companies make available for sale

1. The FDA cannot force a company to make a product available.
2. Companies have production lines. They choose which drugs generate the most revenue, and this is not necessarily the ones that are most needed.

D. Presence or absence of viable alternatives

The recent shortage of fluorescein strips has led some practices to switch to fluorescein in an eye-drop formulation, others to use Tono-Pen or iCare tonometry instead of applanation tonometry to check IOP for selected patients to conserve the supply of strips they have.

II. Reasons for High Prices of Pharmaceuticals in the United States

Market exclusivity / protection by producing companies in order to drive prices lower is a main factor contributing to high drug prices.

A. Initial exclusivity is awarded at the time of FDA approval. Medications are protected for 5-7 years before generic products can enter the marketplace. New biologic agents are protected for 12 years.

B. Extension of patent-related exclusivity. The median length of post-approval market exclusivity is 12.5 years for commonly used medications and 14.5 years for first-in-class medications.

1. Companies can apply for a 5-year extension on patent to account for the time lost during regulatory review and half of the time the medication is undergoing testing in clinical trials. This patent term restoration can last up to 14 years.
2. Testing products in children can lead to an 6 additional months of patent exclusivity.
3. Examples in glaucoma

a. Xalatan was approved June 5, 1996. Generic latanoprost was first available March 22, 2011 (15 years later).

b. Alphagan 0.2% was approved Sept. 6, 1996. Generic brimonidine was first available May 28, 2003 (7 years later).

c. Cosopt was approved April 7, 1998. Generic dorzolamide-timolol was first available Oct. 28, 2008 (10 years later).

C. Other factors contributing to lack of competition even when there is more than 1 brand name product available:

1. The separate roles of the providers who prescribe the medication, the pharmacists who sell the medication, and the patients / insurers who pay for the medications. Physicians are often unaware of the price differential between medications in the same class and so cannot factor that into their decision making. Patients with good insurance coverage are insulated from the price of medications they are receiving. This separation often results in many patients receiving more expensive agents when cheaper, equally effective alternatives are available.
2. Limiting access to generic medications

a. Entry of generics into the marketplace can lead to a substantial decrease in prices. For statins, with 2 generics available, prices dropped to 55% of the brand-name price; with 5 generics, prices declined to 33% of the brand-name price; with 15 generics, prices declined to 13% of the brand-name price.

But generic ≠ more affordable; increased competition = more affordable

b. "Product life cycle management" can delay generic entry. Drug companies make sequential small changes to nontherapeutic components of a drug (coating, formulation) to extend patent life and limit generics from entering the market.

Example in glaucoma: Timoptic was approved in 1978. Approved for all salts of timolol. Betimol (1995) was a hemihydrate (no salts, just timolol + water), so FDA granted it innovator status. Timoptic in

Ocudose got rid of preservatives, so the FDA granted it innovator status. Change to gel-forming solution, change in labeling from twice daily to once daily administration, also led the FDA to grant innovator status (personal communication, Wiley Chambers).

c. Companies producing brand-name medications can offer financial inducements to limit or delay entry of generics by competitors.

d. Backlogs at the FDA can result in 3- to 4-year delays before some generic medications are approved.

e. Lack of availability of raw ingredients and mergers in the industry can limit companies from producing generics.

f. Pharmacists practicing in many states are allowed but not permitted to perform generic substitutions; in some states patients must provide consent to receive generic products. This encourages use of more expensive branded products instead.

g. For some drugs predating the standard drug review process, the FDA allowed some companies to have market exclusivity for inexpensive old drugs, causing prices to skyrocket. For example, the price of colchicine increased 5000% as a result of this.

D. Lack of negotiating power at the national level

1. Countries with national health insurance systems can negotiate prices for drugs and reject coverage of medications that are considered too costly or of low value. In the United States there is no such power.

2. The CMS is able to negotiate or set prices for nearly all services except Part D prescription drugs. Federal law prevents Medicare from securing lower drug prices.

3. Medicaid is required to cover all FDA-approved drugs, even if some are more expensive or confer lower value.

4. In the private sector, prescription benefit management companies and large self-insured employers rarely perform aggressive price negotiations.

III. The Impact of High Drug Prices on Patient Care

A. Cost shifting to patients = higher deductibles and copayments, coinsurance for specialty drugs

1. Higher payments by patients results in patients opting not to fill prescriptions and thus going untreated.[3]

2. Higher payments by patients results in decreased medication adherence.

a. Even a few more dollars in copays can make a big difference.[1]

b. Patients taking branded medications are less adherent than others taking generics.

i. Patients who remained on branded latanoprost were 39% more likely to experience worsening of adherence than others who had been switched to generic latanoprost when it became available.[5]

ii. Lower monthly latanoprost copay was associated with improved adherence.[5]

3. Decreased adherence can lead to worse outcomes.

B. Practices devote a lot of time and energy dealing with approvals so that patients can get the medications prescribed. This time drain can impact patient care.

IV. Potential Ways to Lower Prices for Medications in the United States

A. Encouraging greater competition in the generic market

1. Identifying ways to limit the period of market exclusivity for brand-name medications

2. Limiting secondary patents on products for minor drug changes that do not have a therapeutic benefit

B. Cracking down on companies that pay manufacturers of generic products to delay or avoid entry into the marketplace

C. Reducing costs for research-and-development activities by pharmaceutical companies

D. Limiting costly direct-to-consumer advertising of medications, which can drive up costs

E. Making it easier for generics to enter the marketplace / quicker FDA approval process for generics

F. States can create laws to make it easier for pharmacists to substitute expensive brand-name products with less costly generics.

G. Congress can make it easier to import non-US drugs (eg, if a drug was thoroughly vetted already in the EU and Canada).

H. Authorization of CMS to negotiate prices for Part D plan drugs

I. Increased research and dissemination of results of studies comparing the cost-effectiveness of different treatments

J. Better education of physicians and patients about the comparative costs of different medications so they can make more informed choices about which medications to prescribe or take. EHRs can show price differentials between meds in the same class.

K. FDA can be more proactive at dealing with drug shortages. Presently the FDA plays a role in notifying consumers about shortages, but they offer little to fix things.

V. Alternatives if Glaucoma Medications Are Unavailable or Unaffordable

A. Laser trabeculoplasty is more cost-effective than prostaglandin analogs for patients who have difficulty with medication adherence.[4]

B. Incisional surgery: MIGS, trabeculectomy, glaucoma drainage devices

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Clinical Hallmarks and Natural History of Pseudoexfoliation

John Danias MD PhD

- Pseudoexfoliation syndrome is a systemic condition with eye manifestations.
- Pseudoexfoliation material deposits on various structures of the anterior segment.
- The nature of this material is mostly fibrillar, with fibers made up of microfibrils and coated with amorphous material.
- Ocular manifestations of pseudoexfoliation syndrome include the following:
  - Iris depigmentation
  - Peripapillary transillumination defects
  - Mild trabecular meshwork hyperpigmentation
  - Secondary open-angle glaucoma
  - Phacodonesis or lens subluxation caused by zonular dehiscence
- Pseudoexfoliation is the most common cause of secondary open-angle glaucoma, or pseudoexfoliation glaucoma, worldwide.
- Retinal and optic nerve head pathology of pseudoexfoliation glaucoma is considered to be similar if not identical to that of primary open-angle glaucoma.

Genetic and Environmental Background of Pseudoexfoliation

Janey L Wiggs MD PhD

Introduction

Pseudoexfoliation glaucoma is the most common type of secondary glaucoma worldwide. While the mechanism(s) underlying formation of the disease-related extracellular fibrillar material are not yet known, recent studies have provided a better understanding of the genetic and environmental factors that influence disease risk. In this presentation I will review disease-associated genetic and environmental factors.

Genetic Risk Factors

A genome-wide association study conducted in Iceland identified a robust association of LOXL1 (lysyl oxidase like 1) with exfoliation syndrome.[1] LOXL1 is involved in elastogenesis and collagen crosslinking, which could impact pseudoexfoliation syndrome development by modulating extracellular matrix stability. The associated genetic variants have large effects (odds ratios of approximately 20 in European whites). In European whites and most populations worldwide the disease-associated variants are the common alleles of the risk variants and are present in up to 99% of cases, but also in up to 80% of controls.[2] Collectively, these observations suggest that LOXL1 is necessary but not sufficient for disease development and that other genetic variants and also environmental factors are likely to contribute to the disease development.

Two subsequent genome-wide association studies have been completed for pseudoexfoliation syndrome, and there are now 6 additional genes that are associated with the condition.[3,4] These 6 new genes have much smaller effects on overall risk compared with LOXL1. Recent studies also suggest that LOXL1 genetic modification could be protective.[4]

Environmental Risk Factors

Several environmental exposures may influence pseudoexfoliation syndrome risk. Pseudoexfoliation disease burden increases in extra-equatorial regions, and this distribution is correlated with higher coffee consumption and lower dietary folate, both found to be associated with increased risk of disease. More time spent outdoors is also a strong risk factor for pseudoexfoliation syndrome. This finding suggests that ocular UV exposure could be a contributing factor, and that protection from UV light, especially in childhood, could reduce disease risk.[5]

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How Genetics Translates to Schlemm Canal Outflow: The Role of Microfibrils

Rachel W Kuchtey MD PhD

Exfoliation syndrome (XFS) is the most common identifiable cause of glaucoma. It is characterized by accumulation of exfoliation material (XFM) within the eye and extraocularly. Such deposits within the conventional and unconventional aqueous humor outflow pathways have long been recognized and intensely investigated.[1] An increasing number of new components of XFM have been discovered and studied, although microfibrils remain as the central element.[2]

Microfibrils were first identified over a half-century ago as fine extracellular filaments in the cornea revealed by an electron microcopy study.[3] It is now clear that they are widely expressed protein complexes in the extracellular matrix (ECM) of elastic and nonelastic tissues. Within the complex, a growing number of proteins have been discovered, among which fibrillin-1 is the most abundant.[4] One of the key functions of microfibrils is to serve as scaffold on which elastin cores assemble and, in turn, mature elastic fibers form. Microfibrils play an essential role in terms of the strength, stability, and elasticity of elastic fibers, which is prerequisite to maintain the homeostasis of aqueous humor outflow through the trabecular meshwork and Schlemm canal.[5] In addition to their structural role, microfibrils are equally important in signal transduction, especially through transforming growth factor beta (TGFβ) regulation.[5] TGFβ has long been recognized as a key cytokine in aqueous humor outflow regulation.[6]

Genetic discoveries of microfibril-associated proteins involved in exfoliation glaucoma (XFG) provide more evidence of microfibrils in its pathogenesis. The first identified gene discovered by genome-wide association study (GWAS) to be linked to XFG, *LOXL1*,[7] has strengthened the key role of microfibrils. *LOXL1* encodes lysyl oxidase like -1, an enzyme responsible for crosslinking elastin,[8] which under the proper scaffolding of microfibrils forms elastic fibers. In addition to fibrillin-1 in microfibril complex, other proteins, such as latent TGFβ-binding protein 2 (LTBP2)[9] and ADAMTS10,[10] have been identified through genetic studies as involved in glaucoma. Lastly, *CACNA1A* encoding a calcium channel protein was recently identified through a GWAS as associated with XFG.[11] As microfibril assembly through fibrillin-1 aggregation requires calcium,[12] the discovery of *CACNA1A* adds more evidence in support of microfibrils' involvement in XFG pathogenesis.

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What Makes Exfoliation Glaucoma So Different From Other Open-Angle Glaucomas?

Robert Ritch MD FACS

A long-held false assumption about glaucoma, that open-angle glaucomas (read "varieties, or forms, of open-angle glaucoma") are simply variations on a theme, is finally being dispelled. Exfoliation syndrome (XFS) is a distinct and unique disorder with specific genetic, biochemical, cellular, and pathophysiologic mechanisms.

XFS is not a "risk factor" for glaucoma in the true sense of the term, which I believe needs to be changed. It is a risk factor for trabecular dysfunction and damage, which in turn is a risk factor for elevated IOP, which then is a risk factor for glaucoma. Glaucoma is the most common and important ocular manifestation of what is a systemic disorder affecting many tissues and organs in the body. Exfoliation glaucoma is an ocular manifestation of a systemic disease with multiple ocular and systemic associations. To call it a "form" or "type" of glaucoma is erroneous and distracts us from understanding the mechanisms of the disease, which, in turn, blinds us to new and innovative avenues of treatment.

The first genome-wide association study (GWAS) on XFS, performed in patients and controls from Iceland and Sweden, showed that common genetic variants on the *LOXL1* gene were overwhelmingly associated with the disease. However, a large majority of persons in the general population showed the same variants, including populations in which XFS is uncommon, indicating that *LOXL1* is associated but not causative. In addition, the 2 most common variants differed in Japanese and South African patients. Six additional genes and a rare protective variant allele have since been described from a worldwide GWAS based in Singapore. Environmental and gene-environment interactions also appear to play a role in the development of XFS, including UV light exposure, latitude of residence, increased caffeine intake, and decreased folate intake.

At the cellular level, XFS is characterized by dysfunction of autophagy, a major contributor to multiple age-related diseases throughout the body, brain, and retina. Tenon fibroblasts in 3-D tissue culture are larger in size and proliferate more slowly than cells from patients with primary open-angle glaucoma or controls. Endosomes and lysosomes congregate at the cell periphery rather than migrating to the perinuclear area, apparently due to abnormal binding to microtubules, and mitochondria are depolarized. Reduced clearance of autophagosomes and a decreased ability to degrade misfolded proteins and aging organelles may underlie the development of extracellular protein aggregates in XFS.

Exfoliation material (XFM) clinically consists of a white fibrillogranular material deposited on the tissues of the anterior chamber, most prominently on the anterior lens capsule, where the mature appearance consists of a central zone and peripheral granular zone separated by a clear zone, and on the pupillary border. Physiologic movement of the pupil over the lens results in scraping the XFM from the portion of the lens in contact with the iris, and the XFM disrupts the iris pigment epithelium, resulting in loss of the pupillary ruff and pigment dispersion. It is thought that a combination of XFM and pigment carried to the trabecular meshwork leads to blockage of aqueous outflow and elevated IOP. We have found that 1 drop of 2% pilocarpine q.h.s. can result in a 3-mm nonreactive pupil for 24 hours, minimizing this cycle and preventing blockage of the meshwork.

XFS is the most common recognizable cause of open-angle glaucoma worldwide and elevated IOP is the most common and important ocular manifestation of XFS. However, multiple other ocular disorders have been associated with XFS, including angle closure, cataract, zonular disruption, ocular surface disease, keratopathy, macular degeneration, and retinal vein occlusion. XFS is a systemic disease, associated with ischemia and multiple vascular and elastic tissue disorders. As a result of impaired systemic endothelial function and vascular regulation, XFS is associated with transient ischemic attacks, angina, hypertension, cerebrovascular and cardiovascular disease, impaired cardiovagal regulation, myocardial dysfunction, and coronary artery disease. There is a strong association with hearing loss and a possible association with cognitive dysfunction. Hyperhomocysteinemia is strongly associated with XFS and the associated disorders, but its role in causation remains unknown. Recently investigations into elastic tissue disorders have revealed associations with pelvic organ prolapse, inguinal hernia, chronic obstructive pulmonary disease, and others yet to be reported.

In summary, XFS is a protean disorder which is an ocular manifestation of a systemic disease associated with multiple genes, failure of autophagy, and associated vascular and elastic tissue abnormalities. Only in recent years has its importance been accepted, and newly intensive research is increasingly making surprising discoveries. Non-IOP treatment modalities are potentially applicable at various steps of disease development, which could eventually lead to prevention or reversal of this disease.

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Systemic Manifestations of Pseudoexfoliation

Exfoliation Syndrome

Louis R Pasquale MD

I. Introduction

Exfoliation syndrome (XFS) is categorized by an extracellular accumulation of a heterogeneous group of macromolecules with a core of elastin fibers. The exfoliation material (XFM) is readily apparent in the anterior segment of eye with 10× magnification. The normal histological motif in the human body is that a cellular layer sits on a basement membrane with support from an underlying stromal matrix. I believe that the unique embryology of ocular development contributes to the fairly large accumulations of XFM in the anterior segment. Embryologically, the eye starts as an optic vesicle that invaginates, which creates an alternative structural motif where the basement membrane of cells face fluid-filled cavities. For example, the basement membrane of lens epithelial cells (also known as the lens capsule) faces the anterior chamber. Another example occurs in the ciliary body, where a double layer of epithelium is arranged apex-to-apex with ciliary body stroma on one side and a thin basement membrane on the other that faces the posterior chamber. The latter site often represents a location of considerable XFM accumulation that can be seen on gross inspection. Overall, when a basement membrane is constrained by a cellular layer on one side and a stroma on the other (which is typical in most places in the body), the amount of XFM that can be formed in the extracellular space is more limited. This is important to keep in mind when thinking about systemic manifestations of XFS.

II. Extraocular XFM Deposit Sites

A. Skin

B. Heart

C. Lung

D. Kidneys

E. Blood vessels

III. Do the Extraocular Deposits of XFM Have Clinical Implications?

A. Studies in this space have incredible inconsistencies due to confounding by age and other factors. One well-powered study from India that employed multivariable analysis found that systolic BP was higher in XFS but not high enough to meet a definition of systemic hypertension.

B. Hearing loss: Many studies had suggested that XFS was associated with sensory neural hearing loss, but a recent study found no such associations.

C. Homocysteine (Hcy): Hcy levels are slightly higher in serum, aqueous humor, and tears of XFS patients relative to controls. Hcy is not particularly concentrated in the anterior segment, the most important site of ocular pathology in XFS. Interestingly, rare variants in MTHFR and cystathionine β-synthase (*CBS*) are associated with plasma Hcy levels that can be 10 times the normal level because these patients cannot remove Hcy from the methionine–Hcy cycle. These patients present with severe myopia, ectopia lentis, long limbs, arachnodactyly, hyperlaxity thromboembolism, developmental delay, and intellectual disability, features that are clearly unrelated to XFS. Patients with homocystinuria or CBS deficiency have a shortened life span, but no association between this disorder and XFS has been reported. A 2017 study from India employing a large sample size and multivariable analysis found no relation between serum Hcy and XFS.

D. Pelvic organ prolapse: The Utah Population Database found that XFS was more frequent in women with pelvic organ prolapse, supporting a role for extracellular matrix metabolism in this condition.

IV. Relation Between XFS and Mortality

There are 5 studies showing that XFS is not associated with premature mortality. This calls into question any potential relation between cardiovascular disease, cerebrovascular disease, and XFS.

Overall, XFS is a strongly age-related disease where XFM deposits do occur in extraocular tissues. The manifestations of these deposits are unclear, and there appears to be no reason to work-up XFS patients for systemic conditions.

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Treatment Algorithms of Pseudoexfoliation

Karen M Joos MD PhD

For all steps, need to provide adequate patient education and understanding that pseudoexfoliation is often an aggressive glaucoma with rapid optic nerve deterioration. Engage and partner with the patient—and perhaps the family with permission—to control it.

I. Is the Angle Narrow?

Prevalence about 2.2%.[1] This feature can be missed. Lens subluxation with zonular laxity, posterior synechiae, phacomorphic lens, hyperopia.[2] (Avoid trabeculoplasty to a pigmented Sampaolesi line mistaken as the trabecular meshwork.)

A. If the angle is narrow:

1. Consider laser peripheral iridotomy[1]
2. Consider lensectomy if visually significant cataract.
3. Consider explantation of unstable capsular tension ring and IOL[3]

B. If the angle is open, go to II.

II. Is Ocular Hypertension or Glaucoma Present With Open Angles?

A. Monitor if no ocular hypertension or glaucoma is present, at least annually. The probability of converting to glaucoma ranges up to 50%, and is strongly age-related.

B. Consider treatment if ocular hypertension is present. The Early Manifest Glaucoma Trial (EMGT) showed a more rapid glaucoma conversion rate in subjects with pseudoexfoliation than in subjects without pseudoexfoliation.[4]

C. Treat if glaucoma is present.

1. The screening Thessaloniki Eye Study found the prevalence of glaucoma 3 times higher among subjects with pseudoexfoliation (15.2%) compared to those without pseudoexfoliation (4.7%).[5]
2. The retrospective HMO Maccabi Glaucoma Study found a glaucoma prevalence rate of 40.3% in patients reported with pseudoexfoliation.[6]

D. Treatments

1. Medical therapy (general consensus): Pseudoexfoliation responds less than primary open-angle glaucoma (POAG).
   a. Prostaglandin analogues
   b. Beta-adrenergic antagonists
   c. Alpha-2 adrenergic receptor agonists
   d. Carbonic anhydrase inhibitors
   e. Parasympathomimetic agents (pilocarpine): increased aqueous outflow[7]
   f. Rho kinase inhibitor / norepinephrine plasma membrane transport protein inhibitor: Netarsudil increased trabecular outflow facility and decreased episcleral venous pressure.[8]
2. Laser trabeculoplasty surgery: A better response in eyes with pseudoexfoliation than in eyes with POAG[9,10]
3. Cataract surgery (review of 5 studies): Decreased IOP by 20% and meds by 35% for 34 months.[11] Meta-analysis decrease, 5.5 mmHg, but caution with high loss to follow-up.[12]
4. Incisional glaucoma surgery
   a. MIGS (microinvasive glaucoma surgery) procedures
      i. Trabecular bypass stent: Mean IOP 15.3 ± 1.07 mmHg, mean decrease 35%; meds mean decrease of 1.3 at 6 months[13]
      ii. Ab interno trabeculotomy: Mean IOP 16.1 ± 4.0 mmHg, mean decrease of 12.3 mmHg at 1 year[14]
      iii. Suprachoroidal shunts: No peer-reviewed separate pseudoexfoliation outcomes
      iv. Combined gel stent and cataract surgery: Mean IOP 10.2 ± 3.6 mmHg on 0.9 meds at 6 months[15]
   b. Trabeculectomy: Mean IOP of 11.8 ± 4.4 mmHg at 6 months without antimetabolites.[16] Pseudoexfoliation was more likely to progress to blindness than other diagnoses over 20 years.[17]
   c. Combined trabeculectomy and cataract surgery: Mean IOP 14.2 ± 4.7 mmHg, mean decrease of 6.76 mmHg; meds mean decrease of 2.2 at 1 year[18]
   d. Aqueous drainage devices: No peer-reviewed separate pseudoexfoliation outcomes
   e. Combined endoscopic cyclophotocoagulation and cataract surgery: 30.4% qualified success ≤ 15 mmHg at 1 year[19]

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Tailored Approach to Cataract Extraction in Pseudoexfoliation

Richard K Lee MD

I. Introduction to complications associated with cataract extraction in the pseudoexfoliation glaucoma patient

II. Early recognition of risks for lens and vitreous prolapse

III. Surgical approaches for minimizing cataract surgery complications

IV. Postoperative care of the pseudoexfoliation cataract surgery patient

How Do I Choose the Right MIGS?

Brian A Francis MD MS

I. Glaucoma Surgery: Methods of Action
  A. Transconjunctival filtration
  B. Aqueous inflow
  C. Trabecular outflow
    1. Schlemm canal (SC) dilation
      a. With or without cataract extraction (CE)
      b. Ab interno canaloplasty
        i. 360 degrees of treatment
        ii. Viscodilation of SC with catheter
      c. Visco 360
        i. 360 degrees of treatment
        ii. Viscodilation of SC 180 x 2
    2. Trabecular stents
      a. Combined with CE
      b. iStent (G1 and G2)
        i. (G1) Single trabecular microbypass stent treating up to 2 clock hours
        ii. iStent inject (G2) (FDA investigational device) treating up to 4 clock hours
      c. Hydrus (FDA investigational device): Single stent treating up to 5 clock hours
    3. Trabecular removal or trabeculotomy
    4. SC unroofing
      a. With or without CE
      b. Trabecular removal: Trabectome, Kahook Dual Blade, Goniotome
        i. 180 degrees of treatment
        ii. Removal of strip of trabecular meshwork (TM) and inner wall of SC
      c. Trabeculotomy 360: gonioscopy-assisted transluminal trabeculotomy (GATT), Trab 360
        i. 360 degrees of treatment
        ii. Tearing through TM from SC into anterior chamber (AC)
    5. Trabecular ablation: Trabectome (Neomedix)
      a. First angle-based minimally invasive glaucoma surgery (MIGS) procedure
      b. Plasma energy wave used to ablate the TM
      c. Up to 180 degrees of treatment
      d. Disposable handpiece
      e. Electrocautery generator
  D. Suprachoroidal outflow
  E. Aqueous humor production
    1. Endoscopic cyclophotocoagulation (ECP)
    2. Transscleral cyclophotocoagulation (TCP)
  F. Subconjunctival outflow
    1. External filtration with bleb formation and mitomycin C
    2. Ab interno or external approaches
  G. 360-degree trabeculotomy: GATT
  H. 360-degree trabeculotomy: Trab 360
  I. Trabecular removal: Kahook Dual Blade
  J. Trabecular removal: Goniotome
  K. SC MIGS–Unroofing
    1. TM removal or disruption
    2. Greater area of SC treated
    3. No implant used
    4. Greater tissue disruption
    5. More intraop and postop bleeding
    6. More versatile
      a. Stand-alone procedure
      b. Suprachoroidal outflow
      c. Combined with CE
      d. Suprachoroidal space and uveoscleral outflow
      e. Cypass Stent
      f. Supra Stent (FDA investigational device)

II. Aqueous Humor Production
  A. ECP
    1. Targeted and titratable
    2. Useful in mild glaucoma (with CE) to ultra-refractory (ECP plus)
    3. Endoscope useful for other surgical applications
    4. MIGS
  B. TCP
    1. Cyclophotocoagulation: Reserved for refractory cases with poor visual potential

2. Micropulse
    a. Pulsed laser energy reduces inflammation and complications.
    b. Allows for use earlier in the disease process
3. TCP technique
    a. Contact application with 810-nm diode laser
    b. G probe
        i. Fiberoptic probe applied to ciliary processes externally
        ii. Probe measures fixed distance from the limbus.
        iii. 2000-ms duration with 2000 mWatts power
        iv. 5-6 spots per quadrant
        v. "Pop" is heard, power titrated down 200-250 mW.
4. Cyclophotocoagulation micropulse diode laser
    a. Newest iteration of TPC
    b. Micropulse (Cyclo G6, Iridex Corp.)
    c. Diode 810 nm
    d. Continuous wave laser broken up into short segments
    e. Reduces energy used
    f. Limits thermal build up and collateral damage
    g. Fewer complications
    h. Expands clinical indications
    i. Titrating and repeating treatment

III. Subconjunctival Outflow
A. External filtration with bleb formation and MMC
B. Subconjunctival MIGS or LIGS
C. Xen Gel Stent
    1. Ab interno approach
    2. Tenon left in situ
D. InnFocus microshunt (FDA investigational)
    1. Ab externo approach
    2. Tenon dissection
    3. Xen Gel Stent

IV. Individualizing Glaucoma Surgery
A. Target IOP
    1. Target IOP is based on:
        a. Baseline IOP
        b. Degree of glaucoma damage
        c. Rate of progression
    2. Higher target IOP (mild glaucoma or high baseline)
        a. Trabecular outflow
        b. Aqueous inflow
        c. Suprachoroidal outflow
    3. Moderately low IOP (moderate glaucoma)
        a. Suprachoroidal outflow
        b. Combining MIGS
    4. Lower target IOP (severe glaucoma or lower baseline): Transconjunctival filtration
B. Presence of cataract
    1. Visually significant cataract—consider combined surgery. All options are on the table.
    2. Mild glaucoma with higher IOP may benefit from CE alone.
    3. Combined with MIGS if:
        a. IOP is controlled with multiple meds.
        b. IOP is uncontrolled.
    4. In angle closure cases, remove cataract.
        a. Consider aqueous inflow surgery
        b. Goniosynechialysis alone
        c. Goniosynechialysis combined with trabecular or suprachoroidal
    5. CE may add IOP benefit with MIGS but not with transconjunctival filtration procedures.
C. Type of glaucoma
    1. Primary open-angle glaucoma: All options are on the table.
    2. Pseudoexfoliation glaucoma
        a. Trabecular outflow
        b. ECP may be less effective if pseudoexfoliation material is severe.
    3. Pigmentary glaucoma: trabecular outflow
    4. Primary angle-closure glaucoma
        a. CE, goniosynechialysis + trabecular or suprachoroidal
        b. Aqueous inflow
    5. Plateau iris glaucoma: CE and endocycloplasty
D. Eye considerations
    1. Health of conjunctiva and sclera (scarring, scleral buckle, etc.)
        a. Trabecular outflow
        b. Suprachoroidal outflow
        c. Aqueous inflow
        d. Combined outflow and inflow

2. Intolerance to topical glaucoma medications
    a. Transconjunctival filtration
    b. Combined MIGS
3. Prior glaucoma surgeries
    a. Target a different pathway if prior surgery fails.
    b. If complications arose from prior surgery, avoid repeating.
    c. Patient-specific characteristics
4. Age and life expectancy: Greater age and shorter life expectancy = lower risk tolerance
5. Concomitant disease
    a. Chronic anticoagulation and risk of bleeding
    b. Aqueous inflow < trabecular outflow < suprachoroidal outflow < transconjunctival filtration
6. Risk for infection and hypotony: Avoid transconjunctival filtration and bleb procedures.
7. Patient characteristics: Risk tolerance, lifestyle

CASE 1

- 83-year-old white female patient
- Primary open-angle glaucoma
- Optic nerve (ON) cup-to-disc (C/D): 0.85-0.9 O.D., 0.9 O.S.
- IOP: 14 O.D. (1 med), 23 O.S. (3 meds)
- O.D.: posterior chamber IOL (PC-IOL), O.S. PC-IOL
- Prior Ahmed glaucoma valve O.D.
- Strabismus and diplopia postop
- Ocular surface disease, sensitivity to meds?
- Trabecular ablation and tube shunt removal
- IOP controlled with tube, but with diplopia
- Ocular surface disease and med intolerance could be a problem, but tolerates PF versions
- Moderate to severe ON damage

CASE 2

- 85-year-old white female
- Exfoliation glaucoma
- IOP 24 O.D., 14 O.S.
- PCIOL O.U.
- ON C/D 0.85 O.D., 0.75 O.S.
- O.D.: failed canaloplasty
- O.S.: retinal detachment status post scleral buckle
- Multiple glaucoma drop intolerance, history of asthma
- 2 glaucoma drops, Diamox 250 mg PO b.i.d.
- ECP with trabecular removal
- Moderate to severe ON damage
- IOP high despite oral carbonic anhydrase inhibitors
- Target IOP < 17 mmHg
- PC-IOL
- Patient desire to avoid filtration surgery
- Combining MIGS procedures

V. How to Choose the Right MIGS: Summary

A. Glaucoma surgeon repertoire: MIGS (2 methods of action), transconjunctival filtration (newer and traditional)

B. Must consider

1. Target IOP
2. Cataract
3. Type of glaucoma
4. Eye anatomy
5. History
6. Patient characteristics

Ab Interno Filtration

Manjool Shah MD

I. Introduction
   A. Rationale for choosing filtration procedure in general
      1. Severe disease with low pressure target
      2. Failure of other Schlemm canal– or suprachoroidal-based targets
      3. Concern for significant distal outflow disease
   B. Challenges of bleb-forming techniques
      1. Risk of endophthalmitis, bleb leak, implant exposure
      2. Postoperative management of bleb
      3. Much lower IOP floor, so risk of hypotony; design of gel stent mitigates this risk once past the early postoperative period.

II. Optimization of Ab Interno Filtration
   A. Preoperative management of ocular surface disease and inflammation
      1. Preoperative steroids
      2. Discontinuation of glaucoma medications that may be contributing to inflammation
   B. Patient selection based on facial anatomy
      1. In early cases, avoid patients with:
         a. Tight orbital fissures
         b. Prominent brow and cheek bones
   C. Use of antimetabolites: Mitomycin C injection into subconjunctival space (off-label use)
      1. Small volume (ideally less than 0.1 mL)
      2. Choose concentration based on patient; range: 20-40+ mcg
   D. Ideal location of placement of subconjunctival stent: as close to 12:00 as possible to avoid risk of exposure
   E. Ensuring subconjunctival portion of stent is mobile

III. Postoperative Management

Standard postoperative bleb management

   A. Frequent steroids
      1. Taper once bleb begins to quiet down
      2. Steroid response does occur; can manifest as high IOP with a large quiet bleb
      3. Consider role of additional antimetabolite therapy
   B. Bleb needling
      1. Typically utilized around 1 month postop
      2. With improvements in technique for stent placement, needling rates closer to 20%
      3. Review of needling technique

Ab Externo Microshunt

Iqbal K Ahmed MD

NOTES

Supraciliary Stents: The CyPass Story

Michelle Butler MD

I. Supraciliary / Suprachoroidal Space
   A. Anatomy / physiology of uveoscleral outflow pathway
   B. Previous supraciliary surgeries
   C. Ab externo transscleral cyclodialysis cleft
   D. Ab externo devices: SOLx Gold Microshunt (SOLX, Inc.), STARflo Glaucoma Implant (iSTAR Medical)

II. CyPass FDA Approval
   A. CyPass Micro-Stent (Alcon)
      1. 6.35-mm long polyimide, hollow, flexible, fenestrated tube with a collar and 3 retention rings
      2. Ab interno insertion over a curved guidewire into the supraciliary space
   B. COMPASS Trial
      1. Purpose: To evaluate the 2-year safety and efficacy of CyPass in mild-moderate primary open-angle glaucoma (POAG) patients undergoing cataract surgery
      2. Design: Multicenter randomized control trial enrolling 505 patients with POAG and visually significant cataract randomized 3:1 to phaco+CyPass vs. phaco alone.
      3. Results
         a. Primary endpoint—20% or more IOP reduction after washout: 77% CyPass vs. 60% phaco
         b. Secondary endpoints
            i. IOP reduction: 7.4 mmHg CyPass vs 5.4 phaco
            ii. Achieving IOP 6-18 mmHg: 65% CyPass vs. 44% phaco
            iii. Number of medications: 0.2 meds CyPass vs. 0.6 phaco
         c. Safety
            i. No vision threatening adverse events at 2 years
            ii. Slightly higher incidence of corneal edema (3.5%), transient hyphema (2.7%), iritis (8.6%), hypotony <6 mmHg (2.9%), and IOP spike >10 mmHg (4.3%)
            iii. There were few cases of >2mm cyclodialysis cleft (1.9%), stent obstruction (2.1%), malposition (<1%), and migration (<1%).
   C. The FDA approved CyPass on August 2, 2016.

III. Clinical Experience
   A. CyPass insertion video and description of surgical steps
   B. Postop appearance, gonioscopy photo
   C. Early and late postoperative ultrasound

IV. CyPass Withdrawal From Market
   A. COMPASS XT
      1. Safety data were collected on the subjects who participated in the COMPASS study for an additional 3 years (5 years after surgery)
      2. CyPass group experienced statistically significant endothelial cell loss compared to cataract surgery alone group.
   B. Alcon's letter to physicians, August 29, 2018: "Effective immediately, Alcon has withdrawn CyPass from the market."
   C. FDA notification, September 14, 2018
      1. Recommendations to patients: If you have a CyPass Micro-Stent implanted, you should make an appointment with your eye care provider as soon as possible. Your eye care provider will explain your options and help you decide what to do.
      2. Recommendations to eye care providers:
         a. Do not implant CyPass Micro-Stents, and return unused devices to Alcon.
         b. Review Alcon's recommendations for evaluating and managing CyPass Micro-Stents in patients who have already received the device, such as repositioning or trimming.
         c. At the current time it is not known how endothelial cell density loss might continue to progress more than 5 years after the original surgery, and what impact surgery to remove the device may have on further endothelial cell density loss.

V. Aftermath

Current information will be included at the time of the presentation.

A. Notification of patients: Recommendations from medical malpractice group (OMIC) to be discussed

B. Monitoring patients

1. Awaiting official guidelines on monitoring tests and frequency
2. Document number of retention rings visible on gonioscopy, position of stent, endothelial cell count

C. Surgical intervention

1. Reposition: Tap more posteriorly until only 1 retention ring is visible.
2. Trim: Construct 2 clear corneal incisions under ophthalmic viscosurgical device (OVD). Visualize either directly or with a gonioprism. Hold the proximal portion of the CyPass with microforceps and incise distally with microscissors. Remove the separated proximal portion through the corneal incision. Confirm optimal positioning. Remove remaining OVD.
3. Removal: Fill anterior chamber with OVD, visualize the stent with a gonioprism, grasp with microforceps, observe any traction or tension on surrounding tissues, and gently remove if possible. Remove OVD.

VI. Future

A. CyPass

B. iStent Supra (Glaukos)

C. MINIject (iSTAR Medical)

Angle Surgery

Titratable Goniotomy

Patrick Gooi MD

I. Angle Surgery: Titratable Goniotomy for Glaucoma
   A. 90-120 degree treatment, Kahook Dual Blade
   B. Gonioscopy-assisted transluminal trabeculotomy (GATT) and HEMI GATT modification
   C. Demonstration of 360 blanching from 180 treatment of GATT

II. Surgical Simulation Training
   A. Tackdriver model
   B. SimulEye model
   C. Conclusion

Devices in Canal

Thomas W Samuelson MD

I. Introduction

The Schlemm canal has been at the epicenter of the movement toward the development of safer, less invasive glaucoma surgery. While supraciliary and transscleral options have been added in recent years, the microincisional glaucoma surgery (MIGS) revolution started in the canal. This discussion will review canal devices currently available, as well as those anticipated within the next calendar year.

II. Foundation for Canal-Based Surgery

A. The Role of the Canal in Outflow Physiology

Early versions of canal-based surgery, such as nonpenetrating deep sclerectomy, viscocanalostomy, and canaloplasty, are ab externo approaches widely considered to be safer than traditional trabeculectomy. However, mainstream appeal of such surgery has been limited because it is labor intensive and considerable superior conjunctival and sclera dissections are required, rending subsequent trabeculectomy challenging. Even so, the early work of Robert Stegmann and other advocates of nonpenetrating surgery has played an essential role in the genesis of canal-based MIGS glaucoma surgery, paving the way for current canal procedures.

While research continues to unravel the complex physiology of aqueous humor outflow through the trabecular meshwork (TM), the canal of Schlemm, and the distal outflow system, Johnstone and colleagues have suggested that flow through the circumference of the TM may be nonuniform, divided into high- and low-flow regions, and essentially segmental. The dynamic function of the canal, the degree to which there is pulsatile flow, and the manner in which transcanalicular structures affect outflow physiology raise intriguing questions concerning the potential effect of canal surgery on outflow physiology. Further, it is unclear whether stealth and very localized device placement involving a small portion of the canal circumference is less injurious to normal canal architecture and function as compared to procedures that are ablative and more broadly tissue disruptive. While speculative, one potential advantage of devices within the canal is that canal anatomy and function in other portions of the canal remain anatomically intact. Further, cataract surgery itself lowers IOP, and while the mechanism is speculative, some believe that the effect is from improved physiological outflow. If so, when performing combined phacoemulsification (PE) and glaucoma surgery, efforts to retain TM and canal function may be rewarded long term. Time will tell, but until long-term comparative data are available, I prefer to enhance canal outflow while retaining as much of the canal function and physiology as possible. Localized devices seem well suited to accomplish this.

B. Phacoemulsification and IOP

Numerous retrospective studies have suggested that PE lowers IOP. Such studies were often viewed skeptically due to their retrospective design. Moreover, the IOP-lowering effect of PE is often less evident in large, widely inclusive studies due to the fact that most eyes with physiological IOP do not experience a change in IOP following cataract surgery. When those with elevated IOP are isolated and studied separately, either by stratification or by inclusion criteria in a trial (eg, MIGS trials), the IOP-lowering effect of PE is more readily apparent. Accordingly, the most compelling and seemingly irrefutable data that IOP is lower following cataract surgery are derived from the MIGS trials and the Ocular Hypertension Treatment Study (OHTS). In each of the 5 prospective randomized MIGS trials comparing PE as a stand-alone procedure to PE combined with a MIGS procedure, the control arm has achieved meaningful IOP reduction. It is no longer debatable that PE lowers IOP in patients with ocular hypertension or early to moderate glaucoma. This fact is a cornerstone of the MIGS treatment strategy and provides a compelling rationale to preserve canal function in this population of patients.

Important studies demonstrating that PE lowers IOP:

- OHTS
- iStent US PMA IDE Trial
- Hydrus II
- COMPASS Trial: CyPass US IDE PMA Trial
- Horizon Trial: Hydrus US IDE PMA Trial
- iStent Inject PMA IDE Trial

Advocates of canal-based surgery argue that the favorable effect of PE on IOP provides the foundation for combined glaucoma surgery that may further enhance conventional outflow, reasoning that if PE has a favorable effect on physiologic outflow, why not further enhance canal-based outflow with a safe, minimally invasive approach rather than divert flow to an alternate pathway. Canal *device* advocates prefer a localized approach that is minimally tissue disruptive rather than an ablative or more broadly tissue-disruptive approach. There are enthusiastic advocates for each approach and patient selection, and comparative data are limited.

III. Trabecular-Microbypass Devices

A. iStent

The iStent was developed by Glaukos (Glaukos Corp.; San Clemente, CA), and the first implantation in the United States was performed in 2005.[2] The stent is designed to fit into and remain within the Schlemm canal. Made from non-ferromagnetic titanium, it consists of an inlet (or "snorkel") connected at a 40-degree angle to the half-pipe portion that is implanted within the canal. The stent comes preloaded, attached to the tip of a 26-gauge disposable insertion instrument that has been sterilized by gamma radiation.

The leading, pointed end of the device facilitates entry into the canal, and the direction of this point corresponds to the designation of a right- or left-handed model. Depending on the preference of the surgeon, both "right" and "left" iStents have been developed to ease implantation, although there are no data to suggest that one orientation is more efficacious than

the other. Surgeons are encouraged to use whichever design is more comfortable to implant. The left design is implanted with a forehand maneuver for right-handed surgeons, while the right design is implanted with a backhand maneuver. The segment residing within the canal includes a half cylinder opening, which, combined with heparin coating, helps to prevent blockage or fibrosis. Three retention arches help to ensure that the device will be held in place within the canal. The implant is 1.0 mm in length, 0.33 mm in height, and has a weight of 60 micrograms. The snorkel has a length of 0.25 mm and bore diameter of 120 micrometers.

B. iStent inject

The iStent inject system (Glaukos Corp.; Laguna Hills, CA), a second-generation device, consists of an apical head connected to a narrow thorax that is attached to a wider flange. Currently the smallest medical implant approved for use in the human body, the implant is 360 microns in length, with a diameter of 230 microns. The head is inserted directly into the canal without the need to adjust the angle for implantation or direct it circumferentially. It resides within the canal and contains 4 inlets for fluid passage. The 23-gauge stainless steel injector contains 2 stents for implantation in the nasal angle, at a distance of approximately 30 to 60 degrees. The multifocal placement improves the chance of implanting close to a collector channel, reducing the need for "intelligent placement" (the process of selecting specific anatomic locations within the canal for implantation in the proximity of a collector channel). The iStent inject was approved for use in Europe in 2006 and by the US FDA in June 2018, although it has not yet been commercialized in the United States.

C. Hydrus

The Hydrus Microstent (Ivantis, Inc.; Irvine, CA) is an aqueous drainage device, laser cut from a nitinol (nickel-titanium alloy) tube and thermally set to a curvature consistent with the Schlemm canal. The device is designed for ab interno placement through the TM. While most of the 8-mm device resides within the canal, a portion of the stent remains in the anterior chamber. The device provides a direct inlet to the canal but also scaffolds and tensions the canal. Studies have suggested that such tensioning improves facility of outflow. The fact that Hydrus spans 8 mm, or nearly 3 clock hours, virtually eliminates the need for "intelligent placement" within the canal as it provides access to multiple collector channels. Excellent material biocompatibility has been demonstrated in 2 different in vivo models. Laboratory studies in human cadaver tissue have demonstrated increased outflow facility compared to controls who did not receive the device. The Hydrus implant received European CE mark approval in 2011, and prior clinical studies demonstrated significant reductions in IOP and topical hypotensive medication usage among eyes that received the device, either in combination with cataract surgery or as a stand-alone device, for as long as 2 years postoperatively. The results of the HORIZON Trial were recently published and demonstrate safe and efficacious reduction of IOP that is statistically superior to PE alone, sustained throughout the 2-year study period.

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2018 Advocating for the Profession and Patients

Glaucoma Subspecialty Day

Jeff S Maltzman MD

Ophthalmology's goal to protect sight and empower lives requires active participation and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC® Fund
- Surgical Scope Fund (SSF)
- State Eye PAC

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everyone. The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. At Mid-Year Forum 2018, we honored nine of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Academy's Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both the Surgical Scope Fund and the OPHTHPAC Fund. Each of us has a responsibility to ensure that these funds are strong.

OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy's strategy to protect and advance ophthalmology's interests in key areas, including physician payments from Medicare and protecting ophthalmology from federal scope-of-practice threats. Established in 1985, OPHTHPAC is one of the oldest, largest, and most successful political action committees in the physician community. We are very successful in representing your profession to the U.S. Congress.

Advocating for our issues in Congress is a continuous battle, and OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends among candidates. These relationships allow us to have a seat at the table with legislators who are willing to work on issues important to us and our patients.

The relationships OPHTHPAC builds with members of Congress is contingent on the financial support we receive from Academy members. Academy member support of OPHTHPAC allows us to advance ophthalmology's federal issues. We need to increase the number of our colleagues who contribute to OPHTHPAC and to the other funds. Right now, major transformations are taking place in health care. To ensure that our federal fight and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients.

Among the significant impacts made by OPHTHPAC are the following:

- Secured relief from the burdens and penalties associated with the existing Medicare quality improvement programs for 2018
- Halted applications of MIPS penalties to Part B drug payments to physicians
- Convinced CMS to revisit drastic cuts to retina and glaucoma surgical codes
- Halted the flawed Part B Drug Demonstration
- Derailed an onerous global surgery payment data collection plan
- Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin

Contributions to OPHTHPAC can be made here at AAO 2018, or online at www.aao.org/ophthpac by clicking "Join." You can also learn more by texting "OPHTH" to 51555.

Leaders of the American Glaucoma Society (AGS) are part of the American Academy of Ophthalmology's Ophthalmic Advocacy Leadership Group (OALG), which meets annually in January in Washington, D.C., to provide critical input and to discuss and collaborate on the Academy's advocacy agenda. At the January 2018 OALG meeting, panel discussions took place on the outlook for Medicare reimbursement and implementation of the Merit-based Incentive Payment System (MIPS), as well as specialty research related to the IRIS™ Registry. In addition, meeting participants discussed the changing paradigm for optometric scope battles, held a roundtable to discuss challenges for surgical subspecialties, and considered how telemedicine could impact ophthalmology.

At Mid-Year Forum 2018, the Academy and the AGS ensured a strong presence of glaucoma specialists to support ophthalmology's priorities. Ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The AGS remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund

Thanks to contributions to the 2018 Surgical Scope Fund (SSF) from ophthalmologists across the country, the Academy's Surgery by Surgeons initiative has had a successful year preserving patient surgical safety and surgical standards in state legislatures across the country. The SSF is key to the Academy's Surgery by Surgeons campaign. *If you have not yet made a 2018 SSF contribution*, visit our contribution booth at AAO 2018 or contribute online at www.aao.org/ssf. If you already have made that 2018 contribution, please consider making a crucially needed supplemental contribution.

The SSF provides grants to state ophthalmology societies in support of their efforts to derail optometric surgery proposals that pose a threat to patient safety. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 34 state/territorial

ophthalmology societies reject optometric scope-of-practice expansion into surgery.

To date in 2018, thanks to financial resources from the SSF, the Surgery by Surgeons campaign has netted patient safety and surgery standard preservation victories in the following battleground states:

- Florida
- Iowa
- Maryland
- Mississippi
- Nebraska
- North Carolina
- South Carolina
- Vermont
- Virginia

The 2018 battle is far from over, though. For example, California, Illinois, Massachusetts, and Pennsylvania are currently under assault. Furthermore, as of submission of this update in June 2018, the optometric surgery push had sprouted in six additional states.

Dollars from the SSF are critical in the state surgery campaigns. In each of these legislative battles, the benefits from SSF distributions are abundantly clear. The best lobbyists and public relations consultants are contracted as necessary. Additionally, media campaigns (including TV, radio, and social media) are launched to educate the voting public when needed. This helps to secure success in protecting patient safety by thwarting optometry's attempts to expand its scope of practice to include surgery privileges.

Each of these endeavors is very expensive, and no one state has the resources to wage one of these battles on its own. Ophthalmologists must join together and donate to the SSF to fight for patient safety when a state faces a scope battle over optometric surgery.

The Secretariat for State Affairs thanks the AGS, which joined state ophthalmology societies in contributing to the SSF in 2017, and looks forward to its continued financial support. Ophthalmic organizations like the AGS complete the necessary SSF support structure for the creation and implementation of successful Surgery by Surgeons campaigns.

State Eye PAC

It is increasingly important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the SSF. The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope-of-practice battles and many regulatory issues are all fought on the state level.

ACTION REQUESTED: *Advocate for Your Profession & Your Patients*

Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. State PAC and OPHTHPAC contributions are necessary at the state and federal level, respectively, to help elect officials who will support the interests of our patients. Contributions to *each* of these three funds are necessary and help us protect sight and empower lives. SSF contributions are completely confidential and may be made with corporate checks or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the Surgical Scope Fund, and your State Eye PAC. Please be part of the community advocating for your patients now.

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Surgical Scope Fund	OPHTHPAC® Fund	State EyePAC
To derail optometric surgical scope of practice initiatives that threaten patient safety and quality surgical care	Ophthalmology's interests at the federal level Support for candidates for U.S. Congress	Support for candidates for state House, Senate, and governor
Political grassroots activities, lobbyists, PR and media campaigns	Campaign contributions, legislative education	Campaign contributions, legislative education
No funds may be used for campaign contributions or PACs.		
Contributions: Unlimited	Contributions: Limited to $5,000	Contribution limits vary based on state regulations.
Individual, practice, and organization		
Contributions are 100% confidential.	Contributions above $200 are on the public record.	Contributions are on the public record depending upon state statutes.

The Future of Sensors in the Diagnosis and Monitoring of Glaucoma

Marlene R Moster MD

The minimally invasive glaucoma surgery (MIGS) revolution is now playing a positive role in allowing us to treat glaucoma at earlier stages, as the surgery may afford less risk, with acceptable efficacy. However, even with easier access to these miniature shunts or devices, it is still difficult to know what the individual's pressure is at different times of the day, which is critical in controlling this disease. What happens to the IOP at night, with exercise, and with different medications? An answer to this dilemma is to surgically place an intraocular sensor in the eye to monitor the IOP and finally answer the question, "What really is my IOP?"

This lecture will focus on the evolution of IOP monitoring and how sensors will affect the way we practice ophthalmology in the near future.

TriggerFish Update

Arthur J Sit MD

Intraocular pressure (IOP) has long been known to be variable, with Sidler-Huguenin first reporting diurnal variations in 1898.[1] Post hoc analysis of clinical trial data suggests that IOP variability is associated with a greater risk of glaucoma progression.[2] However, the technology to easily measure 24-hour IOP patterns has been limited.

The Triggerfish contact lens sensor (CLS, Sensimed AG; Lausanne, Switzerland) is the first device to enable noninvasive, continuous, 24-hour monitoring of IOP patterns. The system consists of a silicone contact lens with an embedded strain gauge to measure changes in corneal radius of curvature with changes in IOP.[3] The device is powered and data are transmitted via an adhesive antenna worn around the eye, which is connected to a portable recorder carried by the patient. The device is single-use and is worn for a 24-hour period. Importantly, the device does not measure IOP but rather detects IOP patterns based on the effect of IOP changes on the cornea. The units measured are millivolts from the strain gauge. The CLS was FDA cleared in March 2016 as a de novo device, with the indication "to detect the peak patterns of variation in intraocular pressure over a maximum period of 24 hours to identify the window of time to measure intraocular pressure by conventional clinical methods."

Since the CLS is single use, one of the key questions is whether or not a single 24-hour curve is sufficient, or if multiple curves are required to adequately characterize IOP patterns. Diurnal IOP measurements have been shown by Realini et al to have poor repeatability.[4] However, overall circadian patterns may be more stable than individual IOP measurements at specific times of the day. Mansouri et al.[5,6] have reported that the 24-hour curves from the CLS have moderate repeatability, but this varies for individual patients.

Another key question is whether or not the CLS output is representative of true IOP patterns. Circadian IOP curves measured in a sleep laboratory compared with the CLS curves indicate that the patterns are similar but are not interchangeable. In particular, CLS curves are able to detect the elevation in IOP that occurs from waking to sleeping when measured in the physiologic positions.[7] However, while peaks occur at similar times for IOP and CLS curves, the variations in the 24-hour data for the two techniques do not appear to be correlated.[8]

Recent research with the CLS has focused on identifying patterns that may be useful for predicting disease progression and monitoring therapy. Larger fluctuations have been reported in normal-tension glaucoma patients compared with normal controls,[9] and in primary angle-closure glaucoma patients with progressive disease vs. stable disease.[10] Changes in CLS patterns have been reported in glaucoma patients after treatment with selective laser trabeculoplasty, ab interno trabeculectomy, and ExPRESS shunt.[11-13] Interestingly, De Moraes et al reported specific CLS patterns that were more strongly associated with visual field progression than IOP measured by Goldmann applanation tonometry.[14]

Despite recent progress, further research is required to fully understand the utility of the CLS device in glaucoma management. A large prospective study to identify the patterns that are associated with disease progression would be particularly helpful in clarifying the indications for the device and its clinical value.

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Home Monitoring of Visual Fields

Robert Chang MD

I. The Ideal Visual Field: Glaucoma Detection and Progression Analysis

   A. Guided progression analysis (event- and trend-based) and reducing subjectivity

   B. Deep learning algorithms and determining rate of progression

   C. Home testing: speed and convenience

      1. Moorfields Motion Displacement Test (MBT) on laptop

      2. Experimental head-mounted perimetry to detect multifocal steady-state visual evoked potentials

      3. Melbourne Rapid Fields (MRF) on tablet

      4. Six-month longitudinal comparison of tablet perimeter with Humphrey Field Analyzer:

         Intraclass correlation coefficients (ICC) between MRF and SITA-fast for mean deviation at the 4 visits ranged from 0.71 to 0.88.

How to Use Macular Ganglion Cell Complex Assessment in Your Glaucoma Patients

Kouros Nouri-Mahdavi MD

Macular OCT imaging is now an established technique for evaluating the central and most important part of the human eye's retinal ganglion cell (RGC) complement. About 30% of the RGCs are located within 16° of the foveal center, and the ganglion cell layer (GCL) could amount to 6-7 layers of cells in the thickest area of the macula within 750 to 1100 microns of the foveal center.[1] Several studies have shown that macular RGCs can be affected early during the course of glaucoma.[2] Also, there is evidence that macular OCT imaging may be helpful for monitoring the disease during the later stages of the disease when retinal nerve fiber layer (RNFL) and disc imaging are much less helpful because RNFL and optic disc rim thickness have reached their measurement floor.[3]

OCT devices are different in many ways with regard to macular OCT imaging—most notably, the density of A-scans in the horizontal and vertical axes, area of the macula measured, centration of the macular cube with regard to the fovea, and the outcome (layer) of interest provided. All devices can provide macular full retinal thickness measurements. While Optovue provides the ganglion cell complex (GCC) measurements (the thickness of the inner retina between the inner limiting membrane and the outer boundary of the inner plexiform layer, or IPL), Cirrus high-definition OCT (HD-OCT) measures the combined thickness of the GCL and the IPL (GC-IPL) and Spectralis spectral domain OCT (SD-OCT) can provide GCL-only measurements.

There is no strong evidence that any of these outcomes (ie, GCC, GC-IPL, or GCL thickness) performs better than others for detection of early glaucoma. GCL measurements do not appear to be superior to GC-IPL or GCC at the current level of OCT resolution.[4] Also, structure-function relationships are very similar among various macular outcome measures and comparable to those of RNFL.[5]

Diagnosis

Macular OCT thickness measurements are complementary to RNFL measures with regard to detection of glaucoma damage; that is, they provide additional information in some eyes or they serve to confirm suspicious findings at the level of RNFL or optic nerve head.[6] Similar to RNFL measurements, macular thickness measurements tend to become thinner with advancing age and longer axial length in normal subjects.[7] While age-related changes are accounted for by most SD-OCT devices, axial length is not taken into account.

Eyes demonstrating RNFL damage closer to the temporal quadrant are more likely to demonstrate macular findings. Specifically, eyes with disc damage to an area between the inferotemporal region of the disc and the fovea-disc (FoDi) axis are more likely to demonstrate macular damage. This region is called the macular zone of vulnerability, or MZV.[8] Eyes with normal-tension glaucoma, high myopia, and/or tilted optic nerve heads are more prone to early macular damage.

The most common region of the macula to be involved early in glaucoma is the inferotemporal region. Areas of macular damage can be spotty at the beginning but tend to take an arcuate shape around the fovea with deteriorating disease. The temporal raphe is more or less horizontal regardless of the FoDi axis, and therefore a very helpful early sign of glaucoma is evidence of damage abutting the horizontal raphe on one side. This asymmetry across the horizontal raphe has been found to be a very good indicator of early damage, but clinical software is not yet available.[9]

Detection of Progression

Expansion of the abnormal area and deepening of damage are the most common ways glaucomatous damage progresses. Effective detection of disease deterioration is contingent on high reproducibility of measurements, and macular OCT thickness measurements have been found to be highly reproducible. A change of only a few microns in sectoral or global GC-IPL thickness can represent true deterioration.[10] While Cirrus HD-OCT provides trend and event analyses for GC-IPL measurements, Spectralis OCT provides event analyses only at this point. Macular thickness outcomes reach their measurement floor later than RNFL and neuroretinal rim and hence could be useful in more advanced stages of glaucoma.[11]

Limitations

Eyes with significant retinal damage and distortion due to degenerative myopia are hard to evaluate with macular imaging. Macular diseases are common in the elderly, and any macular disease with significant inner retinal involvement would preclude meaningful imaging of the macula for diagnostic purposes in glaucoma.

Pearls of Macular OCT Imaging

- You may not be able to bill for the extra time and effort of doing macular OCTs, but the effort is well worth it over the long run given its utility as a complementary diagnostic modality.
- Always check the quality factor or the signal strength: it needs to be >6 for Cirrus HD-OCT and >15 for Spectralis B-scans.
- Review the quality of the raw OCT images provided to rule out artefacts. You may need to scroll through the macular cube images.
- Apparent mild ring-shaped thinning of GC-IPL or GCC is fairly common in (highly) myopic eyes.
- Artifacts can appear as areas of thinning or thickening, with clinically unexpected shapes.
- Look for mild thinning in the temporal region (inferior more common than superior) and a sharp horizontal demarcation on the macular pseudocolor map in this area.
- Areas of abnormality flagged in red ($P < 1\%$) are more likely to represent real glaucomatous damage.
- Macular damage is more likely to be real if it is continuous with or adjacent to areas of RNFL damage on OCT.

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What Is the Role of OCT Angiography in Assessing Glaucoma?

David Huang MD PhD

What Is OCT Angiography?

OCT angiography (OCT-A) is a novel imaging modality that uses the motion of blood cells to detect blood flow and map blood vessels down to the capillary level.[1] No extrinsic contrast agent, such as intravenous fluorescein, is needed. OCT-A is a software extension of standard OCT technology and does not require any hardware modification of widely available OCT devices, which are already used extensively in the evaluation of glaucoma and retina diseases. Because OCT-A is noninvasive and economical, it has the potential for routine use in glaucoma diagnosis and monitoring.

What Does OCT-A Measure?

Clinicians already use OCT to measure structural changes in glaucoma, which include thinning of the optic disc rim, peripapillary retinal nerve fiber layer (NFL), and macular ganglion cell complex. OCT-A can be used to visualize and measure the blood vessels in these structures and measure vessel density. In the optic disc, OCT-A has been used to show that glaucoma reduces perfusion both in the superficial disc and in the deeper lamina cribrosa.[2] In the peripapillary retina, vessel density (VD) is significantly reduced in glaucomatous eyes compared to normal eyes, and measuring this could be used to diagnose glaucoma with excellent accuracy, as shown by an area under the receiver operating characteristic curve (AROC) of 0.938.[3]

In the macula, glaucoma damages the ganglion cells supplied by the superficial vascular complex (SVC). OCT-A measurements of the SVC-VD had an excellent diagnostic accuracy for distinguishing glaucoma from normal controls, with a sensitivity of 96.7% and a specificity of 95%, achieving an AROC of 0.983.[4]

How OCT-A Might Improve Glaucoma Evaluation

While both structural OCT and OCT-A can detect glaucoma damage, there are both theoretical and empirical differences in what they show. Structural OCT measures thinning of neural structures, which is associated with the death of ganglion cells and their nerve fibers. OCT-A measures perfusion, which is closely associated with metabolic rate and function. OCT-A may be able to detect dysfunctional nerve fibers or ganglion cells before cell death and tissue thinning occurs—which would allow for earlier diagnosis of glaucoma. A series of articles has shown that OCT-A parameters correlate better with visual field (VF) than structural OCT parameters do.[3-6] Thus OCT-A may be a better surrogate for VF in the evaluation of glaucoma severity and monitoring of glaucoma progression.

In the later stages of glaucoma, OCT-A may be able to monitor progression better than conventional structural OCT measures such as the NFL thickness. The relationship between NFL thickness and VF is highly nonlinear. NFL thins at a high rate, with decreasing mean deviation, in early glaucoma. But because of the presence of residual glial or non-neural tissue, including blood vessels, NFL thickness approaches a floor value in more advanced stages, which is called the "floor effect."[7] Because of the NFL floor effect, NFL thickness measurement is unable to monitor structural progression in moderate to advanced glaucoma. The peripapillary retinal VD has less floor effect and better linear correlation with VF mean deviation.[3,6] Thus, OCT-A has the potential to improve monitoring of progression in moderate to advanced glaucoma.

Summary

OCT-A is a novel, noninvasive imaging technology that allows glaucoma clinicians to evaluate tissue perfusion with high precision, which had never been possible before. OCT-A is implemented on ordinary OCT devices, which are economical and widely accessible. This technology could be used to measure glaucomatous changes in the perfusion of the macular and peripapillary retina. While clinical data on this new technology are still limited, preliminary results show the potential for earlier glaucoma diagnosis and improved monitoring of disease progression rate. Recent advances in commercial instrumentation have made it possible for any clinician to begin using this powerful new tool in their practice.

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Home Monitoring of IOP

Sharon F Freedman MD

I. Why Monitor IOP at Home in the First Place?
   A. Diurnal fluctuations known to have importance in glaucoma progression
   B. Convenience of catching IOPs outside office hours and in "natural setting"
   C. Monitoring for large IOP swings in a postoperative setting that would change treatment

II. Barriers to Home Monitoring of IOP
   A. Danger of corneal injury
   B. Worry about inaccurate information
   C. Cost (time, money) of training and devices to send home
   D. Management of the collected data and need to communicate with patients off-hours

III. Experience in the Pediatric Population With Icare Rebound Tonometry
   A. Comparison of Icare and Goldmann tonometry – calibrating the equipment
   B. Parent / companion training and validation in the office setting
   C. Real-world experience with Icare tonometry in pediatric glaucoma and normal eyes

IV. Taking the Next Steps With Home Tonometry
   A. Investment in the home units; the Icare lending library project (ILLP)
   B. Lack of reimbursement for office, staff
   C. Options for units and data gathering
      1. Icare (standard units)
      2. Icare HOME (storage and cloud-based)
      3. Challenges of EMR data entry

V. The Future of Home Tonometry
   A. Value has been documented in selected cases in adults and children.
   B. Reimbursement system must precede widespread use *but* we need data showing improved outcomes and management in adult glaucoma cases.
   C. A unified approach will be needed, for home tonometry interpretation code.
   D. Future may include insurance coverage also for patient-owned units.
   E. Cost analysis might show decreased need for office visits solely to monitor IOP between imaging sessions for selected patients.

Old vs. New: Gonioscopy vs. Anterior Segment OCT for Narrow Angles and Angle Closure

Sunita Radhakrishnan MD

I. Terminology and Classification of Primary Angle Closure
   A. According to the AAO Preferred Practice Pattern, primary angle closure is characterized by iridotrabecular contact for at least 180 degrees. Iridotrabecular contact is present when the posterior trabecular meshwork is not visible on gonioscopy without compression.
   B. Classification: primary angle-closure suspect, primary angle closure, primary angle-closure glaucoma

II. Gonioscopy
   A. Advantages
      1. Allows quick, 360-degree assessment of the angle
      2. Indentation gonioscopy can be performed and peripheral anterior synechiae (PAS) can be visualized.
      3. Dynamic, illumination-induced changes in the angle can be assessed.
      4. Other causes of elevated IOP can be identified, such as angle recession, pigment dispersion, and neovascularization.
   B. Disadvantages
      1. Requires contact; may artificially widen a closed angle
      2. Requires illumination; may artificially widen a closed angle
      3. Errors in interpretation
      4. Not performed often enough

III. Anterior Segment OCT
   A. Advantages
      1. Noncontact
      2. Can be performed in the dark
      3. Provides snapshot of the anterior segment in 1 scan and the lens position relative to the scleral spur can be assessed
      4. Comfortable for patient and easy to use for operator
      5. Can perform quantitative measurements
      6. Allows assessment of illumination-induced changes in the angle
   B. Disadvantages
      1. Unlike ultrasound biomicroscopy (UBM), OCT does not allow visualization of structures posterior to the iris.
      2. The definition of iridotrabecular contact by OCT is not the same as with gonioscopy.
      3. 360-degree scanning is not practical in routine clinical use.
      4. Scleral spur cannot always be identified.
      5. No quantitative "cut-off" has been determined that can predict risk of angle-closure disease.

IV. Gonioscopy and Anterior Segment OCT in My Practice
   A. I use gonioscopy as the primary method and OCT as an adjunct. The extent of iridotrabecular contact by gonioscopy and the presence of PAS are key to diagnosing and categorizing primary angle closure.
   B. How I Use OCT
      1. To evaluate mechanisms of angle closure
      2. As a patient education tool
      3. In lieu of gonioscopy in patients who cannot tolerate a contact procedure or if corneal pathology limits view to the angle

Assessing the Need for Laser Peripheral Iridotomy in Patients With Asymptomatic Narrow Angles

Hady Saheb MD MPH

I. Review of Angle Closure Classification
   A. Definition of occludable angle
   B. Alphabet soup: PACS, PAC, PACG
II. Natural History Studies
III. Evaluating Risk of Observation vs. Treatment
   A. Progression of disease
   B. IOP spikes
   C. Dysphotopsia
   D. Cataract progression
   E. Corneal endothelial compromise
IV. Relative and Absolute Indications for Laser Peripheral Iridotomy in Patients With Asymptomatic Narrow Angles
V. Practice Patterns for Patients With Asymptomatic Narrow Angles (PACS)

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Utility of Laser Peripheral Iridoplasty in Patients With Narrow Angles Despite Patent Peripheral Iridotomies

David S Friedman MD MPH PhD

I. Defining Angle Closure
   A. Acute attack
   B. Primary angle-closure suspect
   C. Primary angle closure
   D. Primary angle-closure glaucoma (PACG)

II. "Plateau Iris"
   A. Definitions
   B. Ultrasound biomicroscopy definitions and studies
   C. Lack of uniformity in defining the condition

III. Natural History of Primary Angle-Closure Suspects
   A. Low incidence rates even without an iridotomy
      1. Greenland Eskimos low rates
      2. Population-based studies show very few of those with angle closure have glaucoma.
   B. Few develop PACG.
   C. Fellow eyes of acute angle-closure patients have low incidence of disease after iridotomy.

IV. Evidence Limited on Effectiveness of Laser Iridoplasty
   A. Techniques for doing iridoplasty
   B. Prior publications do not show a benefit.
   C. Cochrane review states no known benefit.

V. Balancing Harms and Benefits
   A. No proven benefit of iridoplasty
   B. Iridoplasty is associated with permanent pupil dilation and glare in some patients.
   C. Long-term outcome of untreated residual angle closure is mostly benign.
   D. Iridoplasty not recommended

VI. What Should the Clinician Do, Therefore, if Angles Remain Closed After Iridotomy?
   A. Observe periodically for change in eye pressure
   B. Monitor visual fields
   C. Monitor optic nerve

Clear Lens Extraction in Primary Angle Closure With or Without Glaucoma

Paul Harasymowycz MD

I. Review of Staging of Angle Closure

II. Complications and Effectiveness of Peripheral Laser Iridotomy

III. Publications on Effectiveness of Cataract Surgery or Clear Lens Extraction (CLE)

IV. Case Presentations

The EAGLE Study is a landmark study in the management of primary angle closure (PAC) with an IOP of 30 mmHg or greater, or PAC glaucoma, in which patients were randomized to primary CLE vs. standard therapy including medical management and laser iridotomy. At 3 years, CLE showed greater efficacy and was more cost-effective than laser peripheral iridotomy, and should be considered as an option for first-line treatment.

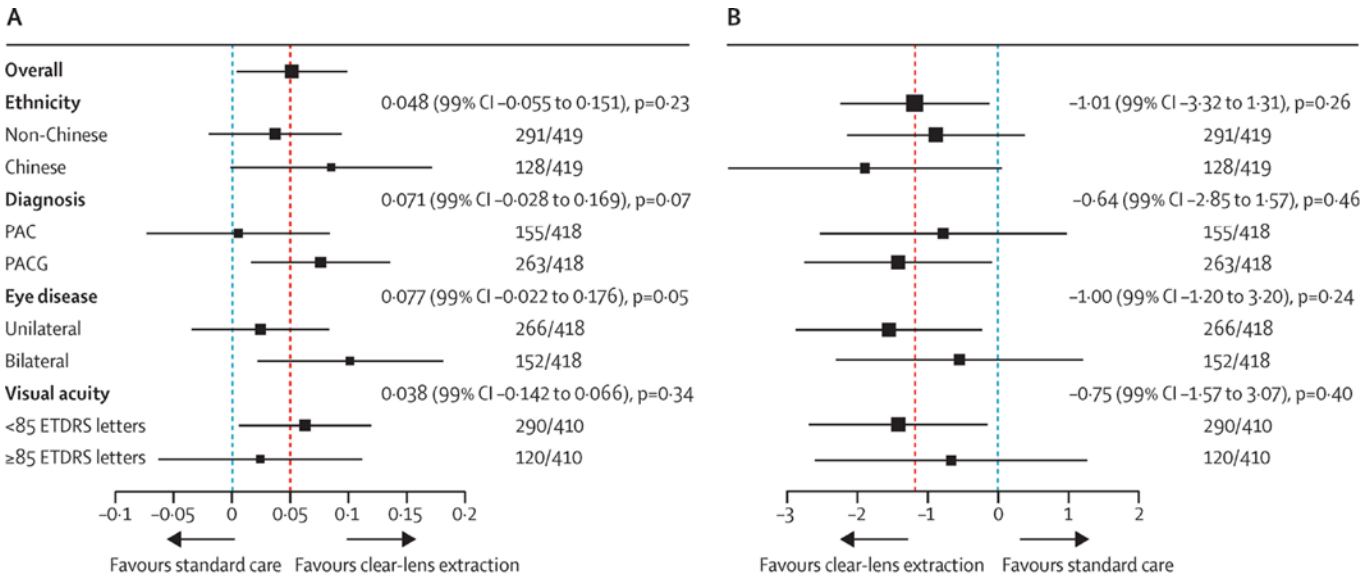

Figure 1. Mean differences in subgroup outcomes between clear-lens extraction (CLE) and standard care. (A) Quality of life scores on the European Quality of Life-5 Dimensions questionnaire. (B) IOP. Red dotted vertical lines—right line in (A) and left line in (B)—indicate overall difference between CLE and standard care. Abbreviations: PAC, primary angle closure; PACG, primary angle-closure glaucoma; ETDRS, Early Treatment Diabetic Retinopathy Study chart.

Role of Goniosynechialysis and Trabecular Bypass Procedures for the Treatment of Angle-Closure Glaucoma

Constance Okeke MD

I. Synechial Angle-Closure Glaucoma (ACG): The Problem

A. In ACG, when there is continued apposition of the iris covering the trabecular meshwork (TM), increased pigmentation of the TM occurs and eventual peripheral anterior synechia (PAS) formation ensues, followed by an elevation in IOP and damage to the optic nerve. A peripheral iridotomy (PI) or even cataract removal[1] may not improve the angle depth or improve outflow if the PAS is significant.

B. When there is extensive PAS and the IOP is uncontrolled, surgical intervention is required.

II. Goniosynechialysis (GSL): A Solution

A. The GSL technique was first reported in1984 by Campbell and Vela and performed in conjunction with cataract surgery.[2] Greater success in IOP control was found when the apposition had not been present for a long period of time (less than one year).

B. Teekhasaenee and Ritch supported findings in a 1999 study of primary ACG (PACG) patients undergoing phaco+GSL within 6 months of angle-closure attack.[3]

1. *N* = 52 eyes
2. Baseline IOP, 29.7 ± 7.9 mmHg
3. Endpoint, 13.2 ± 2.9
4. IOP controlled off medications

C. What is the technique?

The technique is to use viscoelastic to open the angle and maintain the chamber for adequate view while physically teasing away the PAS from the TM under direct gonioscopic visualization utilizing a spatula or microforceps. When performed in conjunction with cataract surgery, GSL can address the root problem by opening a physical obstruction blocking outflow, while the cataract extraction debulks the crowded anterior chamber (AC) for maintenance of outflow.

D. Who is a good GSL candidate?

1. A phakic patient with PAC, PACG, or chronic ACG with elevated IOP and at least 50% of the angle sealed with PAS done with or without cataract surgery
2. Qing et al showed that GSL can be effective alone without cataract surgery.[4]
   a. *N* = 30
   b. GSL with 26-gauge needle
   c. Baseline IOP, 47.1 ± 6.7 mmHg
   d. Endpoint, 17.4 ± 2.2 mmHg after 36 months of follow-up

D. Who is a poor candidate?

1. Neovascular glaucoma
2. Advanced glaucoma with significant cupping and field loss who may not be able to withstand IOP spikes
3. Patients with long-term anticoagulants at risk of hyphema
4. Patients with longstanding PAS

E. What are the pros?

1. In some patients, GSL can provide a safer alternative to trabeculectomy, which removes the possibility of bleb-related leaks or infections.
2. Also, because the conjunctiva is not cut, this leaves room for potential future traditional surgeries.

F. What are the cons?

Some potential complications include development of fibrinous uveitis, hyphema, iridodialysis, and cyclodialysis with resultant hypotony.[3-4]

III. Goniosynechialysis + Phaco + MIGS (Trabecular Removal or Bypass)

A. No studies published to date show date of series for GSL + Phaco + MIGS. It would make sense to believe if GSL + Phaco could increase outflow, then GSL + Phaco + TM removal or bypass would work as well, or even better. Damage to the TM can ensue with prolonged PAS formation. This technique could potentially allow for wider range of successful candidates even with extensive and/or longstanding PAS.

B. Cases

1. Case 1: GSL + Phaco + Goniotomy

   Case presentation and video clip by Dr. Constance Okeke of patient undergoing 180 degrees of GSL with Trabectome tip, followed by 120-180 degrees of TM removal, then cataract extraction

2. Case 2: GSL + Phaco + Trabecular Micro-Bypass

   Case presentation and video clip by Dr. Ike Ahmed of patient undergoing 180 degrees of GSL with microforceps, followed by 2 iStents inserted

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Surgical Pearls for Glaucoma Surgery in Angle Closure

Steven D Vold MD

NOTES

Virtual Reality and Glaucoma

Felipe A Medeiros MD

NOTES

Use of Pluripotent Stem Cells in Glaucoma

IOP Homeostatic Regulation

Mary J Kelley PhD, Diala Abu-Hassan DDS PhD, Xinbo Li PhD, Eileen Ryan BS, and Ted S Acott PhD

The use of stem cell therapies to delay progression, alleviate symptoms, and treat ocular diseases has been of increasing interest to medical researchers, clinicians, and patients as laboratory investigations proceed closer to being developed for clinical use. Although stem cell therapies might include specific endogenous stem cells for a certain eye tissue, or exogenous stem cells such as mesenchymal stem cells, the pluripotent stem cells stand out for their versatility in having the capability to differentiate into any cell type in the body.

IOP and Glaucoma

Although glaucoma is an optic neuropathy, the primary risk factor and currently the only treatable parameter is elevated IOP.

Two types of pluripotent stem cells have been investigated. Embryonic stem cells (ESC) are harvested from the inner cell mass of the blastocyst of an embryo. A newer type of pluripotent stem cell, the induced pluripotent stem cell (iPSC), first made the news in 2006. Takahashi and Yamanaka, working with somatic mouse fibroblasts, overexpressed 4 transcription factors to develop this pluripotent adult stem cell type in the laboratory, and repeated this in human fibroblasts the next year.[1,2]

Among the several advantages that IPSCs appear to have over ESCs, they can be made patient-specific, thereby limiting immune rejection concerns, and they are not generally subject to ethical concerns. Dermal fibroblasts can be harvested from a patient by a simple skin biopsy and then de-differentiated into iPSCs. These iPSCs can then be reprogrammed to become any cell type.[3] In other systems, transplantation of stem cells into tissues or organs has been investigated for regenerative goals where there is cellular loss because of injury or pathology. Additionally, developing disease-specific iPSCs for eye disease modeling in the laboratory to imitate ocular diseases ex vivo can facilitate studies of drug effectiveness for that disease state in a more timely and inexpensive manner, as well as reducing the animal studies needed.[3]

Loss of Cellularity in the TM

Earlier work in primary open-angle glaucoma (POAG) determined that there is a loss of trabecular meshwork (TM) cells in glaucomatous patients. Comparing patients with POAG with age-matched normal individuals established that glaucoma exacerbated the normal loss of TM cellularity with age, and that these differences were highly significant.[4]

Using Stem Cells to Treat Elevated IOP

We hypothesized that increasing the TM cellularity in glaucomatous human eyes could be an effective method to ameliorate the cellular loss observed in glaucoma.[5] Our intent was to make the iPSCs into TM-like cells and transplant them to restore the function of the TM in controlling IOP. After differentiating human iPSCs to TM-like iPSCs and expanding them, we compared the biomarkers of iPSCs, mature TM cells, and differentiated TM-like iPSCs. The differentiated TM-like iPSC markers were nearly identical to those of normal mature TM cells, but the iPSC markers were not.

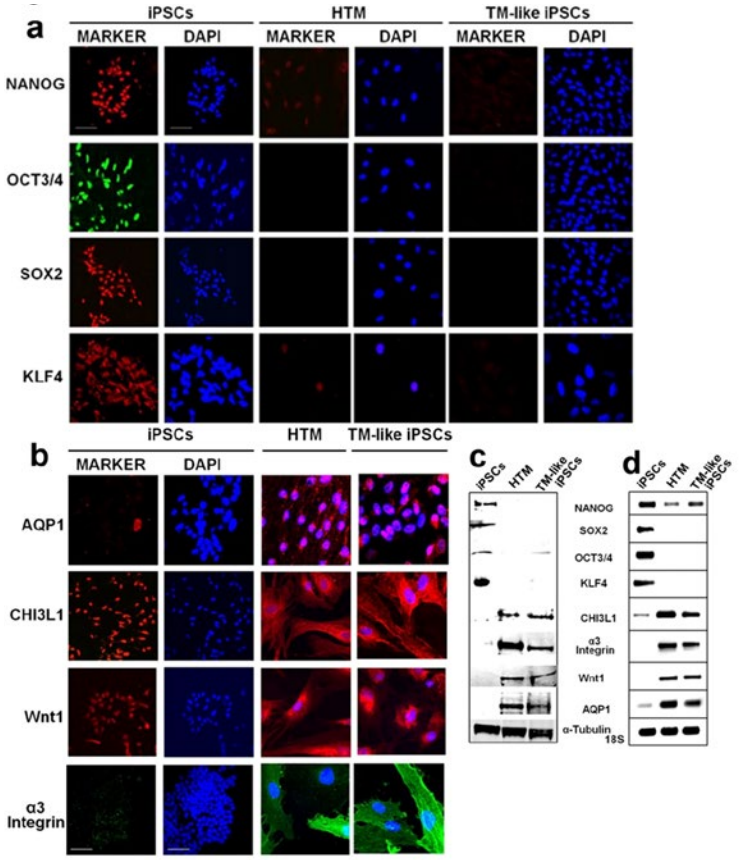

Figure 1. Induced pluripotent stem cells differentiated to TM–like cells have expression patterns similar to those of TM cells.

Human Model for Cell Loss in Glaucoma

To simulate the glaucomatous condition, 0.01% saponin detergent was used to partially denude normal aged human anterior segment preparations of TM cells, approximating the cell loss observed in POAG (see Figure 2).[6] To assay the effect this had on aqueous humor outflow facility, we used the standard human perfused anterior segment organ culture (see Figure 3). Comparing saponin-denuded anterior segments with vehicle controls, outflow did not change, but the ability to mount an IOP homeostatic outflow resistance change in response to a 2x pressure challenge was obliterated (see Figure 4).[6]

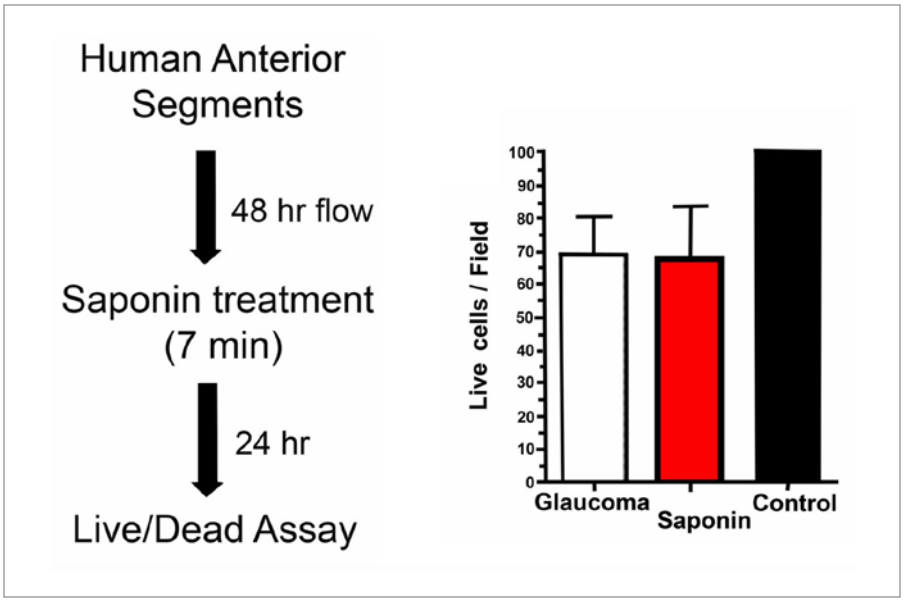

Figure 2. Saponin reduction of TM outflow pathway cell density levels is comparable to that in glaucomatous eyes.

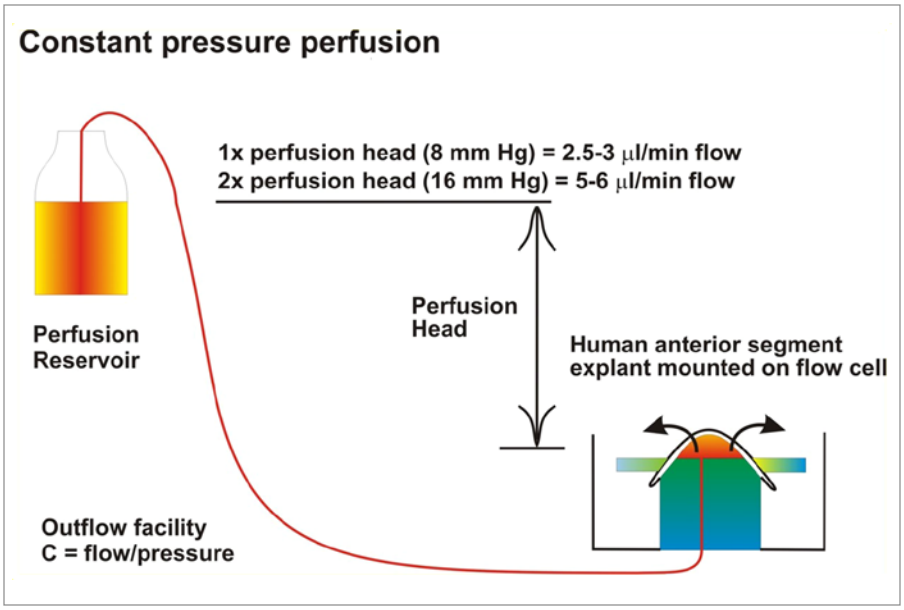

Figure 3. Perfused human anterior segment organ culture.

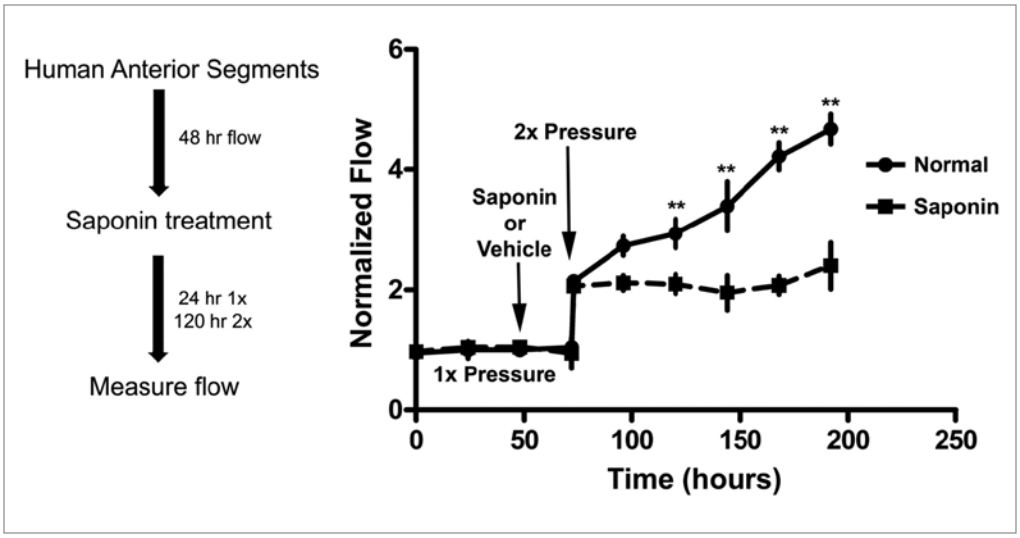

Figure 4. Saponin treatment abolishes the normal IOP homeostatic response to increased pressure.

A normal healthy anterior segment can sense a 2x pressure increase and will adjust the outflow resistance over a few days' time in attempting to correct the IOP, as observed for the control in Figure 4.[7] The saponin-treated anterior segment, being cell-depleted, has lost this homeostatic capability. However, transplanting normal human TM cells back into the denuded anterior segment restored this IOP homeostatic response (see Figure 5).[6]

Transplanting TM-like iPSCs to Restore IOP Homeostatic Function

Differentiated TM-like iPSCs, when transplanted into these denuded anterior segments, were also able to restore IOP homeostatic functionality, while several other cell types, including normal iPSCs, HUVECs, and fibroblasts, were unable to achieve this restoration (see Figure 6).[6]

Integration of Transplanted TM-like iPSCs

Using red quantum dot nanoparticles, TM-like iPSCs were labeled before transplantation to track the extent of integration into the denuded tissue.[6] The transplanted TM-like iPSCs appeared to be integrated into the TM of the denuded anterior segment and were found at all levels of the TM.

Other Investigations

Recently, Kuehn's group used iPSCs to restore IOP control in a mouse myocilin glaucoma model.[8] They achieved significantly reduced IOP and improved aqueous humor outflow facility, which was sustained for at least 12 weeks.[8] Interestingly, they found that only a small percentage of the transplanted cells were present at this time. Importantly, cell contact of the transplanted TM-like iPSCs appeared to trigger increased cell division in the endogenous TM cells.

Stem Cell Transplantation for Glaucomatous TM Cell Loss

These studies support the potential of transplanting differentiated iPSCs to restore IOP homeostatic function to the glaucomatous outflow pathway. This suggests a promising future for using TM-like iPSCs as an innovative, patient-specific treatment for glaucoma.

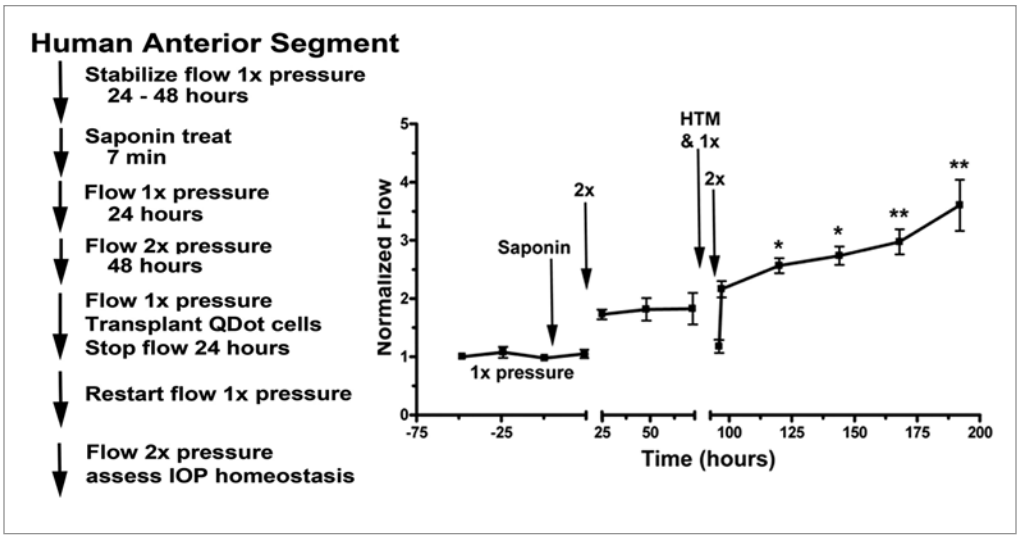

Figure 5. Transplanting trabecular meshwork cells back restores the IOP homeostatic response.

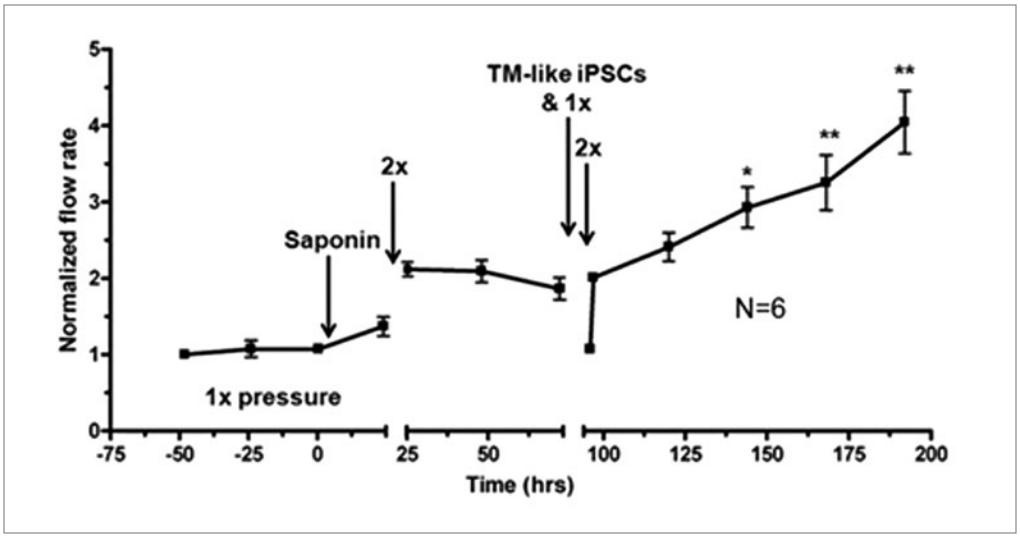

Figure 6. Transplanting differentiated iPSCs also restores IOP homeostatic function.

Stem Cell Clinics

Of rather recent origin is the operation of a number of stem cell clinics, some of which are offering patient treatments for glaucoma. What is the efficacy and safety record of these clinics for innovative therapies to treat your patients?

Future Studies

Although we observed integration of the transplanted TM-like iPSCs into the TM, we have not extensively studied the cell-cell contact and endogenous cell division observed by the Kuehn group in our human model. This will be an important step to examine before moving forward with possible clinical application of this exciting new technology.

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Tele-Glaucoma

Albert S Khouri MD

Benefits

Glaucoma patients can benefit from telemedicine solutions, as many tend to be older and suffer visual loss that can affect their mobility. Glaucoma is a chronic condition that requires ongoing care. Current technology platforms allow for remote screening, diagnosis, and treatment.

Tele-glaucoma has the potential to revolutionize the current health-care paradigm of "first come, first served." Current health-care models do not distinguish between those glaucoma patients who do not need imminent care and others with progressive glaucoma that require timely intervention and health-care access. Tele-glaucoma may convert glaucoma clinical practice to a focus on patients who need close monitoring or intervention.

Tele-glaucoma U.S. and International Initiatives

Several tele-glaucoma clinical studies are ongoing in the United States and internationally.[1-5] The AAO has recognized the value of telemedicine and has sponsored a task force on tele-ophthalmology.[6]

Tele-glaucoma Modalities

Screening vs. consultation, store and forward vs. telepresence: Tele-glaucoma is an integral part of tele-ophthalmology that aims to detect the leading vision-threatening diseases (cataract, glaucoma, AMD, and diabetic retinopathy). Ophthalmic evaluation for visual acuity, noncontact tonometry, and structure (including OCT) and function testing can be mobile, with a small footprint that allows travel to satellite or remote sites. Once data are collected they can be forwarded or shared in real time.

Remote Testing

IOP monitoring has to avoid the use of anesthetics. Current technology is available that allows remote IOP measurement.

- Structure: wearable or handheld technology, table-top imaging systems, software-enhanced imaging[7]
- Functional: computer-based mobile technology and traditional functional testing[8]
- Robotics and artificial intelligence[9,10]

Challenges and Future Directions

Patient retention and follow-up after glaucoma detection is problematic. Many patients do not follow up as recommended. Age, vision loss, and mobility restrictions can hinder traditional glaucoma care. Reimbursement challenges remain an obstacle to wider implementation of tele-glaucoma.

Tele-glaucoma has the potential to remotely diagnose and plan treatment at the time of encounter and has the potential to alleviate some of the obstacles to glaucoma care.

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Metabolic Imaging in Retinal Ganglion Cells

Jeffrey L Goldberg MD PhD

Introduction

Finding novel ways to diagnose, monitor, and treat glaucoma remains a major goal, with unmet needs for clinical care. Working in close collaboration with Alfredo Dubra PhD, associate professor of ophthalmology at Stanford University; Anthony Norcia PhD, professor of psychology at Stanford University; and Vivek Srinivasan PhD, associate professor of bioengineering and ophthalmology & vision science at UC Davis, I have been motivated by the hypothesis that structural and/or metabolic changes in the retina will allow us to detect and monitor glaucoma and evaluate treatment efficacy. The challenge to the field has been the lack of tools sufficient to detect such changes, and indeed the nature of the changes remains opaque.

Mitochondrial Metabolic and Structural Imaging

Mitochondrial changes are among the earliest potential biomarkers of unhealthy ganglion cells and axons, before retinal ganglion cells (RGCs) are irreversibly damaged. Mitochondrial dysfunction has been linked to glaucoma, among many other neurodegenerative diseases. As a key, central player in cellular metabolism, including energy homeostasis and redox / oxidative stress state, the mitochondria remain a prime target as a glaucoma biomarker.

We previously collaborated with colleagues in Japan to use 2-photon imaging in mice to determine the time course of changes in mitochondrial dynamics in response to aging and glaucomatous insults (Takihara, et al, *Proc Natl Acad Sci USA*, 2015). Mitochondria show rapid cessation of movement and other features in response to IOP elevation, and such negative changes are even more dramatic in the aged mouse, consistent with human glaucoma.

Flavin adenine dinucleotide (FAD), a mitochondrial protein that changes fluorescence in response to redox state, is a particular target of interest for in vivo imaging. There is evidence that single-photon fluorescence can reveal FAD and thus metabolic changes. One ophthalmoscope capable of this imaging is based on a fundus camera (OcuSciences). A second approach that allows optical sectioning uses a custom adaptive optics scanning laser ophthalmoscope (AO-SLO) to achieve the maximum axial resolution available to date and improve axial sectioning, resolution, and signal-to-noise ratio.

Structural and Functional Imaging of ON vs. OFF RGCs

Based on the discovery in animal models of glaucoma that early pressure changes lead to preferential disruption to RGC processes located in the outer portion of the inner plexiform layer (the so-called OFF sublayer), we initially investigated whether increment / decrement testing could be used to isolate OFF RGC responses and created a task to make a simple test of a hypothesized ON/OFF pathway degradation asymmetry in glaucoma. Increment and decrement detection is likely to be mediated by separate ON and OFF pathways (Schiller 1986), which begin after the photoreceptors at the bi-polar cell level. Any asymmetry in threshold detection will likely be attributable to a mechanism acting after the photoreceptors. The isolation of the ON/OFF pathways is relevant given the early decay of cells in the OFF pathway discovered previously (Della Santina, et al., *J Neuroscience*., 2013; El-Danaf and Huberman, *J Neuroscience*., 2015; Ou, et al, *J Neuroscience*., 2016; E J Chichilnisky, personal communication).

We have now adapted this approach to use a simple surface electrode set, similar to that used for EEG, to capture data using visually evoked potentials. We are testing this hypothesis in glaucoma patients, glaucoma suspects, and age- and sex-matched controls, comparing against Humphrey visual field, OCT, and other measures. We will also look for changes in response to ciliary neurotrophic factor and nerve growth factor in the 2 randomized controlled trials now initiated in glaucoma patients.

In parallel we are imaging RGC dendrites in the inner plexiform layer (IPL) noninvasively using AO-SLO and OCT. We are exploring reflectivity and layer thickness of the IPL.

Human Subjects Testing

We have been imaging patients using these modalities in 3 parallel trials: (1) a glaucoma cohort trial looking for correlations between visual field loss and RGC metabolic and structural signals in a range of glaucoma suspects, normal subjects, and glaucoma patients; (2) patients randomized to a ciliary neurotrophic factor implant vs. sham surgery in a Phase 2 trial; and (3) patients randomized in a trial comparing nerve growth factor topical therapy with placebo.

Artificial Intelligence and Glaucoma

Investigation of a Deep Learning System in Identifying Glaucomatous Optic Neuropathy Based on Color Disc Photographs

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Introduction

The prevalence of glaucoma is expected to increase to 76 million by 2020 and 111.8 million by 2040. Even though the projected prevalence of glaucoma is increasing, the number of ophthalmologists responsible for diagnosing and treating glaucoma has been stable over the years. Therefore, additional modalities are required to assist ophthalmologists in disease detection, and the use of artificial intelligence (AI) in disease detection, especially in glaucoma screening, has an increasingly larger and more significant role in assisting ophthalmologists in the near future.

AI and Deep Learning Definition

Deep learning is a subset of machine learning that refers to multiple layers of algorithms that allow the program to recognize patterns through the use of artificial neural networks.

Review of AI in Ophthalmology and Glaucoma

The Pegasus Deep Learning System (PDLS), developed by Visulytix, is a deep learning system that seeks to autonomously screen for glaucomatous optic neuropathy by recognizing abnormalities in fundus photography.

Validation of PDLS in Glaucoma

Purpose

To evaluate the performance of PDLS in identifying glaucomatous optic neuropathy on disc photographs.

Methods

Six ophthalmologists with different levels of training evaluated 110 publicly available ORIGA disc images. The reference standard was defined when the 3 graders with highest level of training and better agreement agreed on a binary classification of glaucoma (probabilities > 50%). The PDLS was compared to the reference standard with regard to sensitivity (se), specificity (sp), accuracy (ac), and positive (pv) and negative (nv) predictive values.

Results

The PDLS achieved an AUC-ROC of 83% (bias-corrected 95% CI, 73% to 90%; $P < .05$), with se = 96.1%, sp = 58.3%, ac = 67.2%, pv = 41.6%, and nv = 98.0%. Intraphysician agreement was approximately 86%. Moreover, the graders were more consistent with measuring vertical cup-to-disc ratio (VCDR) than with defining glaucoma, whereas intra-AI agreement was 100% on both the definition of glaucoma and VCDR.

Conclusion

The PDLS had good performance in detecting glaucomatous optic neuropathy on disc photographs when compared to expert graders. In particular, its high sensitivity suggests potential utility for disease detection in glaucoma.

Summary

AI and deep learning have the potential to transform how we deliver eye care and can play a role in blindness prevention.

Schlemm Canal and Collector Channel Imaging

Alex Huang MD

I. Aqueous Humor Outflow (AHO) Patterns

A. Traditionally, AHO is taught using 2-dimensional images (histology or cartoons), including the Schlemm canal (SC) and collector channels (CCs). Thus, when expanded into a 3-dimensional eye, it is implied that AHO is circumferential and uniform.

B. However, there is significant prior data that AHO is segmental, with individual differences and potential disease relevance.

C. Trabecular minimally invasive glaucoma surgeries (MIGS) may be one place where there is clinical and treatment relevance for segmental AHO.

II. Structural AHO Assessment

OCT can identify SC and CCs, but this is sampled data, and the relationship between structural configuration and actual outflow is unclear.

III. Functional AHO Assessment

A. Therefore, we borrow angiographic principles from retina (intravenous fluorescein angiography for retinal blood flow).

B. We develop aqueous angiography in the laboratory using post-mortem human eyes and trabecular bypass.

IV. Functional AHO Assessment in Live Subjects

A. The angiographic camera and operating room setup

B. The nonhuman primate data (segmental patterns, pulsatile nature, and dynamic behavior)

C. The live human data: segmental patterns and validation; overlap of angiographic images with episcleral veins and concurrent OCT showing intrascleral lumens in locations with angiographic signal

D. Video of aqueous angiography in a live human subject showing segmental patterns, pulsatile nature, and dynamic behavior.

V. Functional AHO Assessments to Query Trabecular Meshwork Interventions in Live Humans

A. Sequential angiography with indocyanine green followed by fluorescein in live patients shows similar patterns.

B. Sequential indocyanine green angiography followed by trabecular bypass followed by fluorescein angiography shows improved angiographic signal in regions initially devoid of angiographic signal.

VI. Conclusion

Improved AHO understanding can lead to better basic knowledge and potential clinical utility in either screening for trabecular meshwork pathway drugs or targeting trabecular MIGS for more IOP lowering.

In Vivo Imaging of Apoptosis

M Francesca Cordeiro MD

Clinical trials of new treatments in glaucoma have traditionally relied on IOP as the endpoint. However, the emergence of neuroprotection in glaucoma has led to a need for new measures of treatment efficacy. Several potential outcomes have been suggested, including immunological, genetic, structural, and functional biomarkers.

The identification of in vivo apoptosis could serve as a potential biomarker of disease activity. The technology that has been developed to detect apoptosing retinal cells (DARC) has recently moved from experimental preclinical stages to clinical trials, with Phase 2a trials including patients with glaucoma, AMD, optic neuritis, Down syndrome, and dementia. The Phase 1 results showed that DARC has potential in glaucoma, with significantly greater levels of apoptosis in patients with glaucoma compared to healthy volunteers.

I Tore the PC and See Some Vitreous—Do I Still Do a Planned Ab Interno Angle Procedure?

Here Comes the Vit, There Goes My Angle Procedure?

Arsham Sheybani MD

I. Rates of Vitreous Loss in Cataract Surgery on Glaucoma Patients

II. Rationale for Performing Angle Procedures in Vitreous Loss

- A. Rates of IOP spikes in the postop period
- B. IOP spikes after ab interno angle surgery

III. Considerations

- A. Planned vitrectomy vs. unplanned
- B. Angle surgery and bleeding (vit heme)
- C. Postoperative Pearls

IV. Case Studies (Video Based)

- A. Planned vitrectomy cases
- B. Unplanned vitrectomy cases

Managing Corneal Endothelial Complications of Suprachoroidal Implants

Nathan M Radcliffe MD

Problem

Alcon recently issued a voluntary market withdrawal of their suprachoroidal implant (CyPass) based on 5-year data indicating a higher rate of endothelial cell loss (ECL) in patients receiving cataract extraction (CE) plus the stent vs. CE alone.

Data are forthcoming; however, the 5-year Compass XT data suggest that stent implantation depth is related to the likelihood of ECL, with stents that were not implanted as deeply leading to greater ECL at 5 years, presumably due to stent mechanical contact with the corneal endothelium.

Prevention

While no patients in the 5-year study required corneal surgery, data indicate that a deep implantation, with 1 or fewer rings remaining on the stent being visible in the anterior chamber (AC), is associated with lower ECL rates, while stents with 2 or more visible rings in the AC are associated with higher rates of ECL.

Treatment

Some eyes with >2 rings visible in the AC still did well, but clinically judicious periodic ECL monitoring is advised. Therefore, for eyes with both >2 rings visible in the AC and clinically significant ECL loss over time, a CyPass trimming procedure is recommended with the surgical technique displayed in the video.

Summary

This is the first prospective, randomized 5-year ECL data to be collected on any MIGS implant. It is possible that other MIGS or AC surgical approaches are affected as well, and refractory glaucoma surgical approvals do not typically involve collection of 5-year safety data. The current data and action plan suggest that existing FDA and corporate long-term follow-up studies may be effective in ensuring patient safety after the approval of a MIGS device (ie, the system is working).

How Do I Manage Ab Interno Xen Implantation With Associated Piercing of the Conjunctiva?

Matthew Bryan Schlenker MD

I. An Ounce of Prevention Is Worth a Pound of Cure
   A. Incision planning relative to the cheekbone and speculum
   B. Maintaining an ergonomic / natural position without tension during implantation
   C. Ensuring a long scleral tract

II. Options If You Pierce: Not All Hope Is Lost!
   A. Withdraw hand, reorient Xen more superiorly or more nasally, and then insert.
   B. Continue with insertion, and position Xen away from perforation site.
   C. Continue with insertion, open up conjunctiva at the limbus, and suture Xen away from perforation site.
   D. Consider suture over site, though may not be necessary.

What Goes Up, Might Not Come Down: Closing Hard to Mobilize Conjunctiva After Trab or Tube

Oluwatosin U Smith MD

Traditional glaucoma surgery remains a key portion of our surgical armamentarium in the landscape of evolving minimally or less invasive procedures. A trabeculectomy requires meticulous closure for success, and adequate closure over a drainage implant is necessary for long-term function and structural integrity.

Achieving adequate conjunctival closure may be difficult during both a primary procedure and secondary glaucoma surgery. Occasionally, revision of conjunctival closure is required following initial glaucoma surgery as a result of long-term complications, like bleb leaks or tube exposure. There are varied reasons for difficult conjunctival closure, and some of the risk factors include prior multiple ocular surgical procedures, ocular surface disease, abnormal orbital anatomy, and diabetes.

Difficult conjunctival closure sometimes creates a challenging scenario for the surgeon and in rare instances may warrant an abandonment of the procedure in question for an alternative IOP-controlling procedure.

The use of conjunctival advancement, conjunctival relaxing incisions, contralateral conjunctival autografts, and other means of extensive conjunctival rearrangement at the time of primary closure, as well as conjunctival pedicle flaps, partial-thickness scleral dissection amniotic membrane, and use of collagen glycosaminoglycan matrices at other times are helpful in achieving our endpoints of conjunctiva closure (structural integrity) and control of IOP (function).

A video showing techniques of achieving closure in difficult cases will be shown.

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Managing Intraoperative and Postoperative Blood Reflux With Angle Surgery

Davinder S Grover MD

I. Introduction
   A. The problem with blood reflux in angle surgery
   B. Risk of blood reflux and hyphema related to type of angle surgery
II. Managing / Minimizing Intraoperative Blood Reflux
   A. Maintaining anterior chamber
      1. Viscoelastic
      2. Use of gonioprism
   B. Patient positioning
   C. Wound construction
   D. Blood reflux and episcleral venous fluid wave
III. Managing / Minimizing Postoperative Blood Reflux
   A. Patient behavior and positioning
   B. Treatment
   C. When to wash out
   D. How to wash out
IV. Conclusion: Take-home Points

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