DECODING GLAUCOMA: FROM MECHANISMS TO MANAGEMENT

JESSICA STEEN OD, FAAO, DIPL ABO

1

JESSICA STEEN OD FINANCIAL DISCLOSURES

- Speakers Bureau-Carl Zeiss Meditec, Bausch and Lomb, Viatris, Thea Pharma, Alcon, Allergan, Astellas, Dompé
- Consultant-Bausch and Lomb, Balance Ophthalmics, Carl Zeiss Meditec, Opus Genetics, Viatris, Allergan, Astellas, Alcon, Radius XR, iCare, Glaukos, Eyenovia, Tarsus, Orasis, Topcon, Envision Health Technologies, LKC
- Shareholder-Clearside Biomedical, Annexon Bio (<0.01% ownership)
- *All relevant relationships have been mitigated*

2

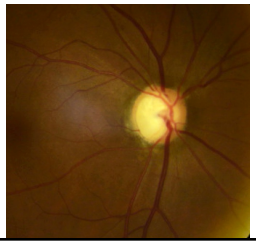
The foundation of assessment: optic disc evaluation

We're really talking about assessment of the neuroretinal rim

Best assessed binocularly at the slit lamp using a magnified view

4

The health of the neuroretinal rim is NOT assessed by a cup to disc ratio



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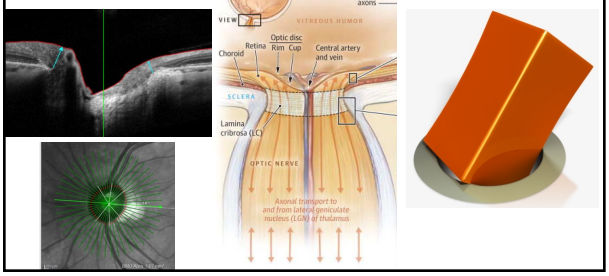

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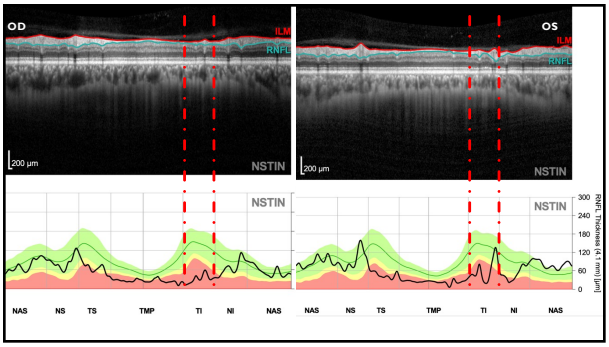
7


A different patient!
58 year old Black male

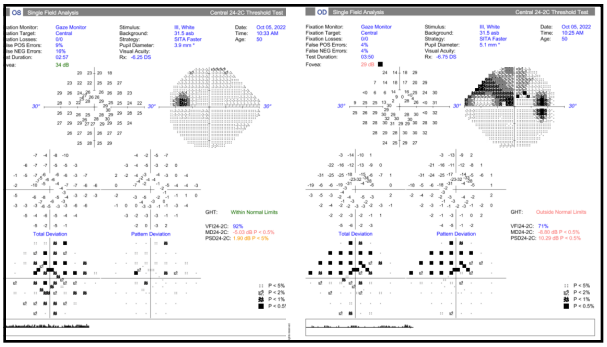
8


51 year old Black male
Peak IOP 24mmHg/34mmHg
CCT 535/525 µm
Brimonidine-timolol BID OU
Netarsudil-latanoprost QHS OU

9


OD
OS
ILM
RNFL
200 µm
NSTIN
NAS
NS
TS
TMP
TI
NI
RNFL Thickness (4.1 mm) [µm]

11



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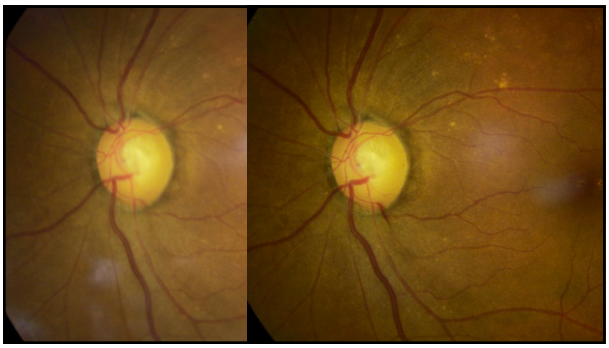

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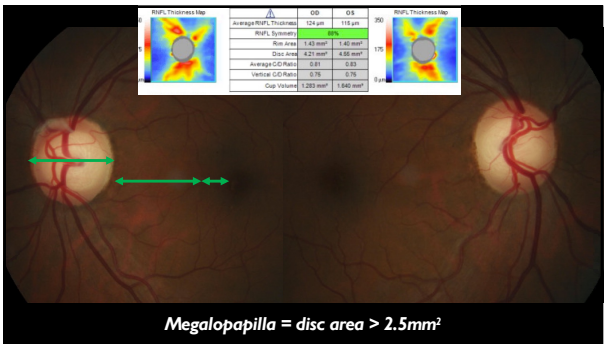
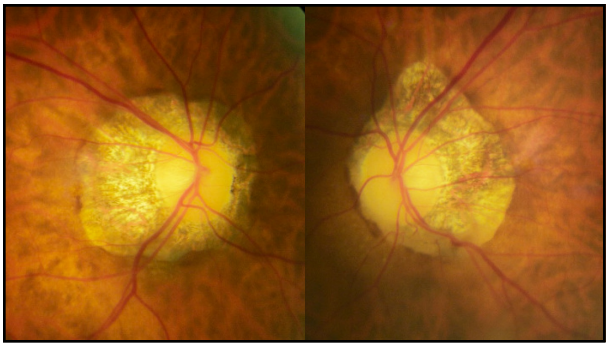

Megalopapilla = disc area > 2.5mm²

20



21

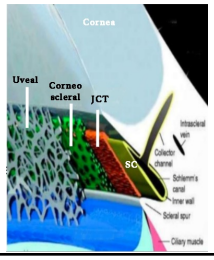
Peripapillary atrophy or "halo"

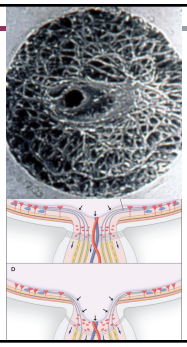
Nerve fibers are susceptible to damage when they are passing bare choroid

These eyes may be more sensitive to pressure changes--and this halo can enlarge and change over time

22

Where does glaucoma live?

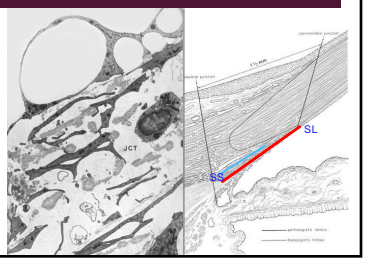




23

HISTOPATHOLOGY OF GLAUCOMA

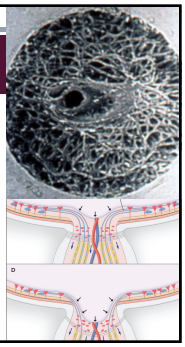
- Accelerated and exaggerated normal aging changing in the anterior chamber angle
- Increased resistance to outflow occurs at the level of the juxtacanalicular tissues in the trabecular meshwork and inner wall of Schlemm's canal
  - Detachments of endothelial cells produce giant vacuoles
- Cell turnover every 3-4 days



24

HISTOPATHOLOGY OF GLAUCOMA

- Posterior segment
  - Compression of laminar sheets
  - Distortion of laminar pores
  - Posterior and lateral displacement of laminar sheets
  - Blockage of axonal transport
  - IOP (mechanical) and vascularly induced death of ganglion cells
  - Deepening (backward bowing) and enlargement of the optic cup due to loss of ganglion cells



25

Goal is disease modifying therapy

Based on understanding of how disease happens

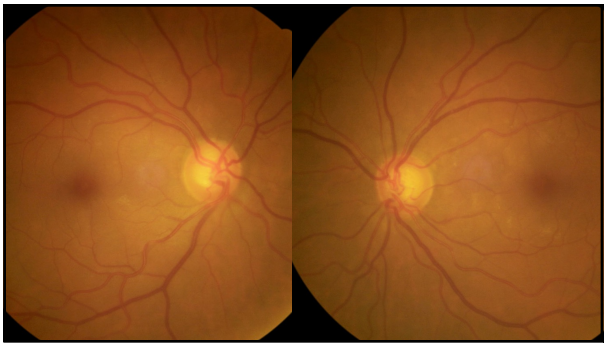
Interrupt pathophysiology

26

57 YEAR OLD FEMALE

- Referred for evaluation of suspicion of glaucoma
- Her son was diagnosed with glaucoma at the age of 11
- Medical history
  - Type 2 diabetes mellitus (A1c 6.2%)
  - Cervical cancer
  - Breast cancer
- BCVA 20/20 OD and OS
- IOP 20mmHg OD 25mmHg OS
  - CCT 482/487 µm

27



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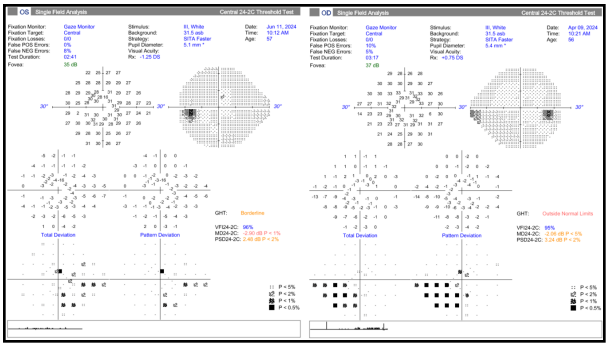


29

Now the focus shifts to identification of progression

We've improved in reducing incidence of glaucoma-related blindness

Prostaglandin analogs

Risk of blindness due to POAG vs. angle closure glaucoma

30

Once a patient is determined to be stable

How frequently do we follow patients?

How frequently do we perform testing?

31

How often do we perform testing?

It depends on how we may best (most quickly) be able to detect change

Pachymetry: once**

Gonioscopy: Every 1-2 years
Necessary for diagnosis

32

OCT Evaluation of the Anterior Chamber

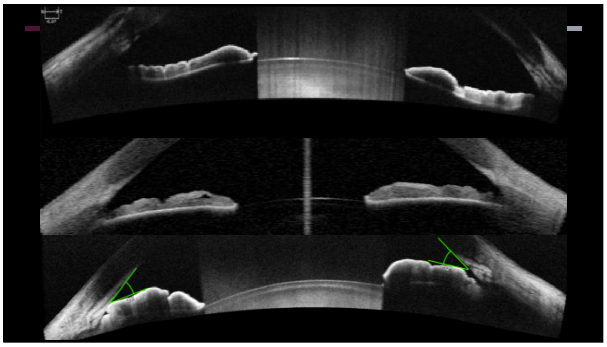
Not a replacement for gonioscopy

No inadvertent compression

May be performed in complete darkness

Most valuable to determine if the angle is open or closed

33



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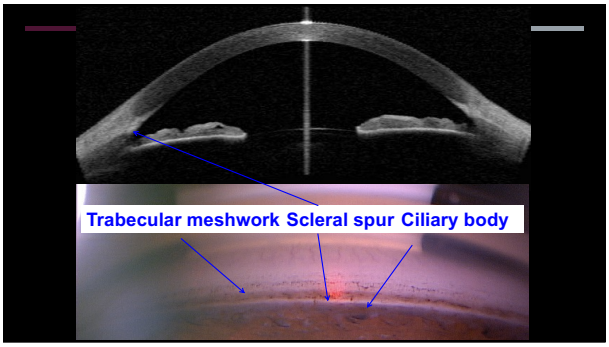


35

73 year old female

History of POAG; diagnosed in her 40s, treated with topical medications

"small bottle and a big bottle with a blue cap"

IOP consistently in the 30-40mmHg range despite treatment

IOP 42mmHg OD 28mmHg OS

36

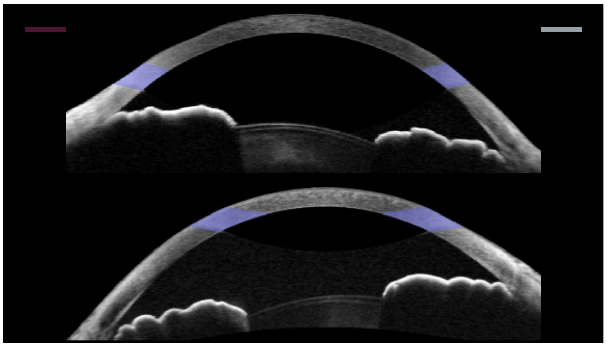
Gonio Examination:

OD
Superior: OD SUP: no structure seen
Nasal: OD NAS: no structure seen
Temporal: OD Temp: no structure seen
Inferior: OD INF: no structure seen

OS
Superior: OS SUP: no structure seen
Nasal: OS NAS: open to anterior TM
Temporal: OS TEMP: no structure seen
Inferior: OS INF: open to anterior TM

Comment: appositional touch OD and OS; convex iris approach OD and OS, with very difficult compression no AR, NVA OD and OS
1-2+ PTM pigment with compression OD and OS.

37



38

Frequency of visual field testing

Practical recommendations for measuring rates of visual field change in glaucoma

B C Chauhan,[1] D F Garway-Heath,[2] F J Goñi,[3] L Rossetti,[4] B Bengtsson,[5] A C Viswanathan,[2] A Heijl[5]

Br J Ophthalmol 2008;**92**:569–573. doi:10.1136/bjo.2007.135012

6 visual fields within the first 2 years—to identify "fast" progressors

466+/- 232 days

Bradley C, Herbert P, Hou K, et al. Comparing the accuracy of peripapillary OCT scans and visual fields to detect glaucoma worsening. *Ophthalmology*. 2023; 130: 631–639

39

OCT

Frequency of Optical Coherence Tomography Testing to Detect Progression in Glaucoma

Bruna Melchior, MD,† Carlos G. De Moraes, MD, PhD, MPH,* Jayter S. Paula, MD, PhD,† George A. Cioffi, MD,* Christopher A. Girkin, MD, MSPH,‡ Massimo A. Fazio, PhD,‡ Robert N. Weinreb, MD,§ Linda M. Zangwill, PhD,§ and Jeffrey M. Liebmann, MD**

(*J Glaucoma* 2022;31:854–859)

40

Comparing the Accuracy of Peripapillary OCT Scans and Visual Fields to Detect Glaucoma Worsening

Chris Bradley, PhD,[1] Patrick Herbert, BA,[2] Kaihua Hou,[2] Mathias Unberath, PhD,[2] Pradeep Ramulu, MD, PhD,[1] Jithin Yohannan, MD, MPH[1,2]

DESIGN FOR OPTIMAL PREDICTION IN SIMPLE LINEAR REGRESSION*

D. W. Gaylor and H. C. Sweeny
Research Triangle Institute 1965

"Therefore, multiple OCT or VF measurements, or both, should be obtained during the same visit whenever possible, even at the expense of longer intervals between visits."

41

Glaucoma is a syndromic condition.

Progressive ganglion cell axonal loss which leads to characteristic visual field damage

"Related" to intraocular pressure

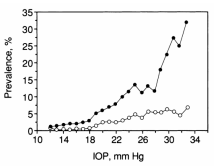
At least 30% of POAG presents with statistically normal IOP

Some secondary impact of increased pressure sensitivity

42

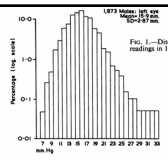
Intraocular Pressure

- This is the most significant risk factor overall
- IOP which is statistically abnormal is not necessary physiologically abnormal for an individual eye
- Conversely, IOP that is statistically normal is not necessarily physiologically normal for an individual eye
- **There is no clinically useful level of IOP to differentiate all normal from all people with glaucoma**



African American subjects, n = 4674 (closed circles; Caucasian subjects, n = 5700 (open circles)

43



Brit. J. Ophthal. (1966) **50**, 570

FIG. 1.—Distribution of applanation pressure readings in 1,873 male left eyes.

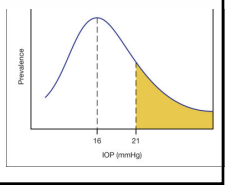
INTRA-OCULAR PRESSURE, GLAUCOMA, AND GLAUCOMA SUSPECTS IN A DEFINED POPULATION*

BY

F. C. HOLLOWS† AND P. A. GRAHAM

Epidemiological Research Unit and Department of Ophthalmology, Royal Infirmary, Cardiff

- "Normal tension glaucoma" "Primary open angle glaucoma with statistically normal pressure"
- "Average" intraocular pressure is 15-16mmHg (SD = 2.5mmHg)
- "Normal" range 11-21mmHg
  - Based on a population-based study in Wales of nearly 2000 white males over 40 years of age



44

What other risk factors exist?

Elevated IOP
Older age
Black or African race or Latino or Hispanic ethnicity
Family history of glaucoma
Thin central corneal thickness
Low ocular perfusion pressure
Myopia
Type 2 diabetes mellitus
Low systolic and diastolic blood pressure
Hypothyroidism
Migraine
Sleep apnea
Peripheral vasospasm (Raynaud's syndrome)
Cardiovascular disease
Low corneal hysteresis
Systemic hypertension
Low cerebral spinal fluid pressure
Genetics

46

Glaucoma and genetics

At least 296 loci have been identified (Han et al. 2023)

In most patients, complex genetics are involved

Each gene contributes a small amount of risk, but none of which cause disease on their own

- ***Direct contribution to disease development***
- ***Influence biological pathways***
- ***Contribute to other risk factors (IOP)***

Polygenic risk score; one more parameter to consider

47

Glaucoma and genetics

"Genetic risk score service"

Commercially available tool(!!)

Seonix Bio-SightScore

Based on 7 million genetic variants

49

Understanding the biology sets the stage for understanding the therapeutic approach

56

Original Investigation

September 7, 2023

39% higher odds of having glaucoma; not IOP-dependent

Calcium Channel Blocker Use and Associated Glaucoma and Related Traits Among UK Biobank Participants

Alan Kastner, MD, MSc[1,2]; Kelsey V. Stuart, MBBCh, MSc[1]; Giovanni Montesano, MD[1,3]; et al

» Author Affiliations | Article Information

JAMA Ophthalmol. 2023;141(10):956-964. doi:10.1001/jamaophthalmol.2023.3877

62

AMERICAN ACADEMY OF OPHTHALMOLOGY®

In partnership with the AMERICAN GLAUCOMA SOCIETY

Association of Systemic Calcium Channel Blocker Use with Visual Field Progression in a Large Real-World Cohort from Glaucoma Clinics

Giovanni Montesano, MD, PhD,[1,2] Alessandro Rabiolo, MD,[3,4] David F. Garway-Heath, MD,[1] Dun Jack Fu, MD, PhD,[1] Gus Gazzard, MD,[1] Giovanni Ometto, PhD,[1,2] David P. Crabb, PhD,[2] Anthony P. Khawaja, PhD, FRCOphth[1]

Slower rate of visual field progression in those treated with calcium channel blockers—"likely not clinically significant".

63

Medication innovation

1873-2018

Has there been a development which interrupts pathophysiology?

65

IOP LOWERING MEDICATION OPTIONS

- First line treatment:
  - Prostaglandin analog
    - Best adherence at FDA approved dosing
- What does 'maximum medical therapy' mean?
  - ***Classically***:
    - 1) Prostaglandin analog
    - 2-4) CAI
      - Alpha-2 agonist
      - Beta blocker
    - Rho kinase inhibitor
    - ?Pilocarpine

66

Prostaglandin analogs

Greatest adherence at FDA approved dosing

Increase uveoscleral outflow
(Small effect on conventional outflow)

67

"NEW" PROSTAGLANDINS

- Latanoprostene bunod 0.024% (Vyzulta)
  - Latanoprost acid + butanediol mononitrate
    - Butanediol monohydrate releases NO which increases outflow through the trabecular meshwork and Schlemm's canal
      - Relaxes trabecular beams
- Latanoprost 0.005% preservative free (Iyuzeh)

68

Nitric oxide

Relaxes smooth muscle

Increases spaces between trabecular beams

Is there any impact on neuroprotection?

69

ORIGINAL INVESTIGATIONS

Effect of Latanoprostene Bunod on Optic Nerve Head Blood Flow

Samaha, Dan OD, MSc, FAAO[1]; Diaconu, Vasile PhD; Bouchard, Jean François PhD; Desalliers, Charlene OD; Dupont, Ariane OD

Author Information

Optometry and Vision Science 99(2):p 172-176, February 2022. | **DOI:** 10.1097/OPX.0000000000001842

Increased blood flow volume and oxygen saturation vs. latanoprost in healthy subjects

70

RHO KINASE

- Rho kinase family includes proteins which regulate cell shape, motility, proliferation, and apoptosis
  - **Regulate smooth muscle contraction in the trabecular meshwork and ciliary body**
- *May also affect ocular blood blow and retinal ganglion cell survival*
  - *Role in cardiovascular procedures, corneal procedures*
  - *Role in development of fibrosis*

72

Rho kinase inhibitors

Trabecular meshwork tissue in eyes with glaucoma is stiffer

CLAN (cross-linked actin networks) formation—what is the impact on CLAN formation?

Steroids increase CLANs and increase outflow resistance

73

RHO KINASE INHIBITOR/NOREPINEPHRINE TRANSPORT INHIBITOR

- **Increase trabecular outflow**
- **Lower episcleral venous pressure**
- Netarsudil 0.02% (Rhopressa)
  - QHS
- Netarsudil/latanoprost 0.02%/0.005% (Rocklatan)
  - QHS
- Hyperemia-most common effect
  - Typically improves over time
  - *When do you see your patients back after altering medical therapy?*
- Subconjunctival hemorrhage
- Less common-corneal verticillata
  - Level of the epithelium

74

Unmet needs in glaucoma management

Nocturnal IOP lowering

Neuroprotection…

What about nicotinamide?

80

Nicotinamide and Pyruvate for Neuroenhancement in Open-Angle Glaucoma

A Phase 2 Randomized Clinical Trial

Carlos Gustavo De Moraes, MD, MPH, PhD[1]; Simon W. M. John, PhD[1,2,3]; Pete A. Williams, PhD[4]; et al

Author Affiliations | Article Information

JAMA Ophthalmol. 2022;140(1):11-18. doi:10.1001/jamaophthalmol.2021.4576

ARVO Annual Meeting Abstract | June 2024

Restoration of Blood-Retinal Barrier Integrity Prevents Neurodegeneration in Glaucoma

Isaac Alejandro Vidal Paredes; Jorge Luis Cueva Vargas; Nicolas Belforte; Yukihiro Shiga; Florence Dotigny; Heberto Quintero; Adriana Di Polo

ARVO Annual Meeting Abstract | June 2024

A Phase 1 Trial of Topical Insulin for Patients with Glaucoma

Zac Wennberg Smith; Gala Beykin; Mariella Saludares; Mariana Nunez; QianQian Wang; Adriana Di Polo; Jeffrey Louis Goldberg

81

Neuroprotection (and neurorecovery?!)

Translation from RGC culture models → experimental models → RCTs

Mitochondrial dysfunction drives RGC degeneration (mouse)

NAD (precursor of nicotinamide) demonstrated to be neuroprotective in mice (Williams 2017)

Ongoing clinical trials—target enrollment over 1300
Swedish Nicotinamide Trial: newly diagnosed OAG; 3g oral nicotinamide without standard IOP-lowering therapy

Primary endpoints 20 months or longer; safety: liver function (ALT, AST, and bilirubin)

82

American Glaucoma Society-American Academy of Ophthalmology Position Statement on Nicotinamide Use for Glaucoma Neuroprotection

Aakriti Garg Shukla, MD, MSc, George A. Cioffi, MD, Simon W.M. John, PhD, Qing Wang, MD, PhD, Jeffrey M. Liebmann, MD, on behalf of the American Glaucoma Society and American Academy of Ophthalmology

Accepted Date: 7 January 2025

300 patients dosed across trials; 2 have developed drug-induced liver injury

73 year old woman with POAG and normal liver function

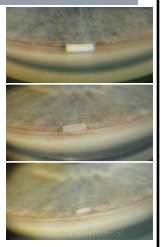
69 year old Chinese woman in Singapore; BMI 15

Changed study protocol to LFT at baseline, 1 week, 2 months, 4 months, every 4-6 months

83

Sustained release

Bimatoprost implant 10mcg



Sustained release bimatoprost
Equivalent to about 2-3 drops of bimatoprost 0.01%
Drug release complete in 3-4 months

197 eyes, 94.9% pseudophakic, 41.6% prior SLT, mean age 80.4
Effect approximately 1 year; reduction in medication use
16.9% underwent SLT within first 12 months

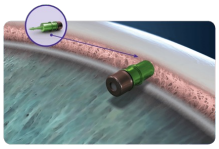
No corneal edema related to implant observed

Teymoorian S, Craven ER, Nguyen L, Werts E. Real-World Study of the Effectiveness and Safety of Intracameral Bimatoprost Implant in a Clinical Setting in the United States. Clin Ophthalmol. 2024 Jan 19;18:187-199.

85

Sustained release

Travoprost titanium implant (75mcg)
FDA approved December 14, 2023
Not refillable



36 month data: 70% (fast-release) and 68% (slow-release) fewer or same medications as baseline

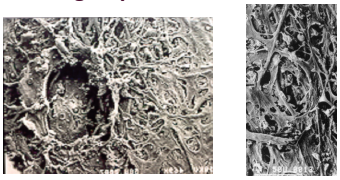
Mean IOP reduction: 8.3mmHg (fast-release) and 8.5mmHg (slow-release)

Berdahl JP, Sarkisian SR Jr, Ang RE, Doan LV, Kothe AC, Usner DW, Katz LJ, Navratil T; Travoprost Intraocular Implant Study Group. Efficacy and Safety of the Travoprost Intraocular Implant in Reducing Topical IOP-Lowering Medication Burden in Patients with Open-Angle Glaucoma or Ocular Hypertension. Drugs. 2024 Jan;84(1):83-97.

86

SLT

Targets melanin-causes less tissue destruction and wound healing response vs. ALT



87

SLT

Champagne bubbles = explosions at the microscopic level

…this is tissue damage

Damage to TM endothelial cells which allows for new cells to migrate from Schwalbe's line over about 1 week post-treatment

Leads to macrophage recruitment and TM proliferation

88

Is SLT disease modifying?

iovs investigative ophthalmology & visual science — Leading clinical and laboratory ophthalmology and vision research — ARVO

Invest Ophthalmol Vis Sci. 2015 Nov; 56(12): 7100–7108. PMCID: PMC4634628
Published online 2015 Nov 3. doi: 10.1167/iovs.15-17660 PMID: 26529044

Profiling of Cytokines Secreted by Conventional Aqueous Outflow Pathway Endothelial Cells Activated In Vitro and Ex Vivo With Laser Irradiation

Jorge A. Alvarado,[1] Phuonglan Chau,[1] Jianfeng Wu,[1] Richard Juster,[1] Amde Selassie Shifera,[2] and Michael Geske[1]

89

Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial

Gus Gazzard, Evgenia Konstantakopoulou, David Garway-Heath, Anurag Garg, Victoria Vickerstaff, Rachael Hunter, Gareth Ambler, Catey Bunce, Richard Wormald, Neil Nathwani, Keith Barton, Gary Rubin, Marta Buszewicz, on behalf of the LiGHT Trial Study Group*

No game-changing data; But did provide good quality evidence for what was already known

SLT: at target 93% of visits, 91.3% in the medication group (3 years)

90

Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial

Six-Year Results of Primary Selective Laser Trabeculoplasty versus Eye Drops for the Treatment of Glaucoma and Ocular Hypertension

Conclusions: Selective laser trabeculoplasty is a safe treatment for OAG and OHT, providing better long-term disease control than initial drop therapy, with reduced need for incisional glaucoma and cataract surgery over 6 years. *Ophthalmology 2023;130:139-151 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

No difference in health-related quality of life scores: mobility, self-care, usual activities, pain or discomfort.

Minimal difference in Glaucoma Symptom Scale-did not translate to difference in HRQoL

91

ARTICLE IN PRESS

Six-Year Rate of Visual Field Progression in the Laser in Glaucoma and Ocular Hypertension Trial

Giovanni Montesano, MD, PhD,[1,2] David P. Crabb, PhD,[2] David F. Garway-Heath, MD, FRCOphth,[1] David M. Wright, PhD,[1] Evgenia Konstantakopoulou, PhD,[1,4] Neil Nathwani, BSc (Hons), DipTp(IP),[1] Giovanni Ometto, PhD,[1,2] Gus Gazzard, MD, FRCOphth[1]

Results: Data from 710 eyes (482 with OAG and 354 in the SLT-first arm) were analyzed. The 2 arms had similar baseline MD ($P = 0.7$). The average intraocular pressure (IOP) during follow-up was 16.1 [14.2–18.2] for the drops-first arm and 16.8 [14.6–18.6] in the SLT-first arm (median [interquartile range], $P = 0.057$). The mean [95% credible interval] MD rate was −0.37 [−0.43 to −0.31] decibels (dB)/year in the drops-first arm and −0.26 [−0.31 to −0.21] dB/year in the SLT-first arm ($P = 0.007$). When stratified by severity, this difference was significant only in mild OAG ($P = 0.035$, the largest sub-group). The secondary analyses largely confirmed the main results. The difference in MPD rate was also significantly slower in the SLT-first arm ($P < 0.001$).

26% of med-first eyes were fast-progressors vs. 15% in SLT-first

92

JAMA Ophthalmology | Original Investigation

Selective Laser Trabeculoplasty After Medical Treatment for Glaucoma or Ocular Hypertension

Evgenia Konstantakopoulou, PhD; Gus Gazzard, MA, MD, MBBChir; David Garway-Heath, MD; Mariam Adeleke, PhD; Gareth Ambler, PhD; Victoria Vickerstaff, PhD; Catey Bunce, DSc; Neil Nathwani, BSc; Keith Barton, MD; for the LiGHT Trial Study Group

Patients were randomized to SLT or medication first (LiGHT)-then after 3 years patients were allowed to have secondary SLT (to reduce medication load) or to escalate therapy if needed

65% of 320 subjects taking drops chose to continue medical therapy!

93

What's next?

Low-energy Selective Laser Trabeculoplasty Repeated Annually: Rationale for the COAST Trial

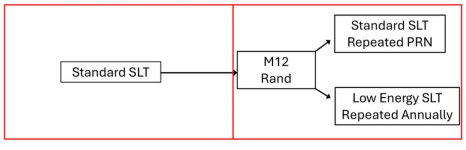
Tony Realini, MD, MPH, Gus Gazzard, MD,†‡ Mark Latina, MD,§ and Michael Kass, MD§‖*

Estimated primary completion date: June 2027

Aims to determine optimal energy level and frequency of SLT

94

Determined that initial low energy (0.4mJ) SLT was not as effective as initial "full strength" SLT starting at 0.8mJ



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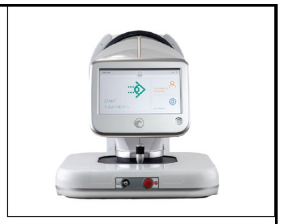


Direct SLT-no lens used! 1.7mJ

120 shots, 3ns duration, 400 micron spot size, 2 seconds (GLAUrious trial)

96

Filtration surgery

Progression happens.

44% of OAG patients demonstrated need for escalation in therapy in the first 4 years after diagnosis

30% of those require a second modification

Cumulative risk of blindness increases to 13.5% at 20 years

97

WHAT'S ON THE MIGS MENU?

- Non-bleb forming
  - Inflow
    - Transscleral cyclophotocoagulation
  - Outflow
    - Implant (stent)-iStent inject, iStent inject W, iStent infinite, Hydrus
    - Excision of tissue-Trabectome, GATT, Kahook dual blade
    - Dilation of tissue-canaloplasty
  - Bleb-forming (*ab interno* implants)-e.g. Xen Gel Stent

99

MIGS

2 iStents are "better" than 1

3 iStents = similar IOP lowering in comparison to goniotomy

Challenging to interpret and apply data

IOP reduction? Or fewer number of medications?

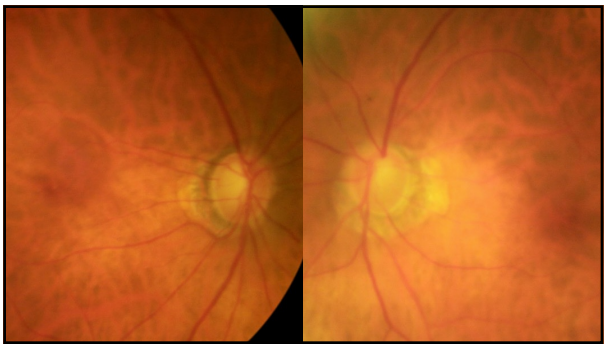
Important to understand and communicate goal with operating surgeon

100

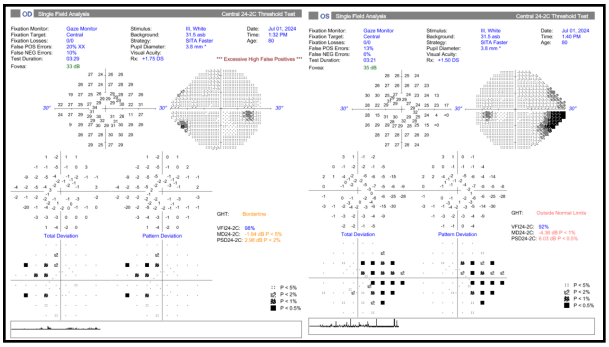
80 YEAR OLD FEMALE

- Diagnosed with bilateral POAG moderate stage in 2013
- Peak untreated IOP 22mmHg OD 23mmHg OS (CCT 562 µm OD, 568 µm OS)
  - Medically managed with the use of timolol, travoprost, latanoprost, brimonidine, brinzolamide, brinzolamide/brimonidine over the last 12 years
  - Currently taking latanoprost 0.005% QHS OU
- History of breast cancer (remission since 2015), hiatal hernia, type 2 diabetes mellitus
- BCVA 20/30- OD and OS (BAT 20/60 OD and OS) with nuclear sclerosis
- Treated IOP 14-17mmHg; target IOP 16mmHg or less OD and OS

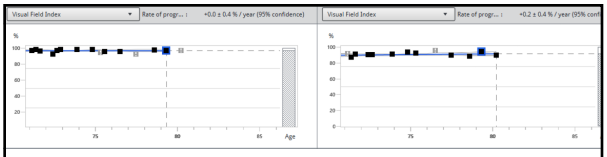
102



103



104



Goals

1. *Maintain IOP without topical ocular medication*

2. *Only interested in what will be covered by Medicare*

105

Putting it all together

How does this impact and guide clinical decision making?!

106

Bottom line

We know more about glaucoma pathophysiology than we sometimes give ourselves credit for

Take the time you need to establish a diagnosis and when making treatment decisions

Understand the impact of therapeutic selection on the bigger picture

125

Jessicaa.steen@gmail.com
480.289.0613

126