Glaucoma – REVISED

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1

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2

Financial Disclosures

- Speaker for Shire

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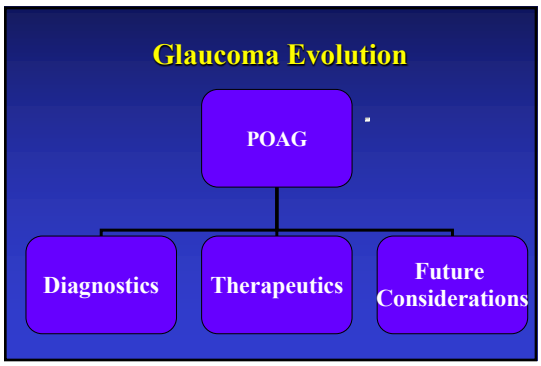
3



4

Glaucoma Evaluation is Transforming

- In the past, detection & management relied on functional assessment
  - Visual fields (white-on-white)
    - Insensititve for detecting early POAG
    - High degree of variability
- Recently, structural change over time longitudinal studies have validated the role of structural imaging
  - Are structural defects with normal functional tests false positives or POAG?

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5

Glaucoma Evaluation is Transforming

- Glaucoma considered a NOCTURNAL disease
- IOP increases starting at bedtime and stay high all night
- Concept of "flattening the curve" of IOP
- New emphasis on sleep apnea link to POAG
  - Blood flow issues
  - Sleep lab studies
- Ocular blood flow
  - Systemic medications worsen blood flow to head
  - CMS temporary code for measuring ocular blood flow

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6

24 Hour Contact Lens Sensor

- Weinreib, Mansouri, Romenet
- Accurate and reproducible method to measure nyctohemeral IOP rhythm
- "Triggerfish"
- Significant rhythm detected
- Nocturnal disease nature of glaucoma
  - Highest IOP at 4 am
- Sleep lab studies in Obstructive sleep apnea
- Consider especially in low tension glaucoma

7

Triggerfish / Sensimed, Switzerland

- Received FDA approval for 24 hr metrics to assess IOP, peak IOP, fluxuation, and allow customized timing of drop application (chronotherapy, IOP modulation)
- Measures change of corneo-scleral not IOP in mmHg
  - Correlates well with IOP
  - CLS output may reflect changes that are more relevant to glaucoma damage than pure IOP
- Single use CL records 300 data points for 30 seconds at 5 min intervals transmitting them wirelessly to antenna worn around eye, then onto a recorder around neck

8

Pachymetry 76514

- Bilateral
- Measurement of central corneal thickness (CCT) proven by Ocular Hypertension Treatment Study (OHTS) to be standard of care in diagnosis and management of glaucoma, glaucoma suspect and ocular hypertension
- Also billable for keratoconus, corneal transplants, cataracts with corneal dystrophies, guttata, edema
- Requires Interpretation & Report
- Fee $11.92

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9

Pachymetry

- Risk of POAG conversion in OCHTN is 11% (OHTS) in 5 years
- Risk is greater if CCT is THIN
  - 36%
  - Thin is <555um
- Thin corneas are an independent risk factor in OCHTN
- Thin corneas have not yet been found to be an independent risk factor for POAG

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10

Pachymetry

- IOP correction by correlation to corneal thickness is NOT POSSIBLE!
  - A linear relationship does not exist!
  - Careful examination of regression analysis (scatter graph of IOP relative to CCT) demonstrates huge bandwidth
- Adjusting IOP by CCT instills a degree of accuracy into an inaccurate measurement
- It is possible to adjust the IOP in the WRONG direction
- Barbados study of black patients shows no correlation of CCT/IOP
- "Trying to be more precise than this is not supported by the data and may be harmful to patient care" Jamie Brandt, MD Dir Glauc Src, UCD / OHTS investigator

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11

Corneal Compensated IOP (IOPcc)

- 7CR Autotonometer – Reichert
- Pressure significantly less affected by the cornea than other instruments
  - Hysteresis is a risk factor for glaucoma
- Incorporates bidirectional applanation technology used in ORA, to quantify biomechanical properties of cornea
- Non contact (air puff) simultaneously provides a Goldmann-correlated (IOPg) and IOPcc
- Helpful in patients with cornea disease and glaucoma

12

Corneal Hysteresis 92145

- Unilateral or Bilateral
- Corneal hysteresis determination by air impulse stimulation
- Requires Interpretation & Report
- Fee $ 15.37

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13

Multifunction Tonometer – Falck Med

- Tonometry
  - Slit lamp mounted, applanation
  - 60 automated measures/3 sec
  - No NaFL, no mire
  - Disposable single use prism
- Ocular Pulse Amplitude – systolic/diastolic waveforms
- Tonography – measures outflow resistence
- Ophthalmodynamometry (ODM) – pulsatile force of CRA
- Model – FAT1 Multifunction tonometer

14

i-Care Tonometer

- Hand held, portable
- NO ANESTHESIA
- Disposable probe
- Accurate
- Power – AA batteries
- Measurement in 0.1 sec
  - Measures motion of cornea
- Digital display
- Memory – last 10 results

15

i-Care Tonometer

- Applications
  - Eye MDs
  - ODs
  - General practitioners
  - Pharmacy
    - Screenings
  - Veterinarians
  - Consumers
    - Self screenings

16

Glaucoma Pipeline

- Extracellular Matrix metalloproteinases
- Oral neuroprotectants - Memantine (Nameda)
- Sustained release formulations
  - Punctal plugs
  - Injectable implants
- Home IOP monitors – 24 hr monitoring
  - Mansouri & Weinreib used telemetric contact lens sensor
  - IOP doesn't behave the same in individuals right/left eye
    - Monocular therapeutic trials have been invalidated
  - IOP not conserved from day to day

17

Glaucoma Pipeline

- Combined structure-function index (CSFI) – new paradigm
  - Unlike VF testing alone, performs well in detecting pre-perimetric glaucoma
  - Unlike imaging alone, successful at discriminating early vs moderate and moderate vs advanced glaucomatous damage
  - Reported as a % of loss of ganglion cells
  - Detects progression better than other indicies
    - CSF I= 22%, VFs = 8.5%, OCT = 14.6

18

Glaucoma as a Two Pressure Disease

- Intracranial space and intraocular space are two fluid filled compartments separated by the lamina cribrosa
  - If pressure on one side (IOP) matters than why wouldn't pressure on the other matter?
  - CSF pressure begins to drop after age 40-50, same time when glaucoma prevalence increases
  - ICP lower in patients with normal tension glaucoma & high tension glaucoma compared to normal
  - ICP is lower in normal tension vs high tension glaucoma
  - Theory is laminar deformation caused by translaminar pressure difference of IOP & ICP
    - Squeezes axons of RGC's as they travel through nerve
    - Disrupts axonal transport leading to cell death
- Glaucoma is multifactorial and IOP is only one factor

19

Glaucoma Pipeline

- Intracranial cerebrospinal fluid pressure (CSF-P) is lower in glaucoma
- Trans-laminar pressure difference (TLPD)
  - TLPD = IOP – CSFP (normal is 4-8mmHg)
  - Lumbar measurements not as accurate as orbital CSF-P
  - MRI offers high resolution of optic nerve diameter (OND) and sheath diameter (ONSD) and optic nerve subarachnoid space width (ONSASDW)
    - Is a reliable predictor of CSF pressure

20

Evolving Views on IOP

- IOP is a causal risk factor in development of glaucoma at all levels of IOP
- IOP plays a role in every eye with glaucoma
- Knowledge of IOP is not necessary to diagnose or detect progression in glaucoma
- What aspects of IOP behavior is most responsible for glaucoma progression?
  - Mean IOP/ Peak IOP/ we don't know!
- Home tonometry is coming into practice and will help identify patterns of IOP
- Ocular perfusion pressure (OPP) is a risk factor for development of glaucoma (low OPP)
  - Difference between systemic BP & IOP

21

Evolving Views - Angle Closure Glauc

- Prevalence of PACG is growing substantially
  - By 2020 it will affect 23 million
  - By 2040 it will affect 32 million
  - PACG is less common but more severe and likely to cause irreversible blindness
- Standard traditional therapy is peripheral iridotomy and topical eye drops to reduce IOP
- Should surgical lens extraction be considered given a perfectly healthy lens is an open question?
- EAGLE study – Effectiveness in Angle closure Glaucoma of Lens Extraction
  - 5 countries compared safety, efficacy and cost effectiveness of clear lens extraction vs iridotomy as first line treatment

22

Evolving Views - Angle Closure Glauc

- Unquestionable advantage to clear lens extraction for all measures
  - Mean IOP 1.18 lower in lens group
  - Self reported health status improved
  - While initially more costly, if was more cost effective over 3 & 10 years
  - Fewer subsequent procedures
  - Less burdensome medications
- Challenges the conventional standard of care
- Particularly important in areas like Asia, east Asia, where PACG is the predominant form of glaucoma
  - As well as where health care resources are limited
  - Azuara-Blanco Lancet 2016; 388 (10052) 1389

23

Visual Field 9208x

- Bilateral
- Requires Interpretation
  - separate report form
  - narrative in body of medical record, on date of service
- Fee $43.88- (-81) $57.37+ (-82) $65.92- (-83)

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24

FDT Perimetry Abnormalities as Predictors of Glaucomatous VF Loss

- 105 eyes of 105 glaucoma suspects
  - IOP 23mm+ or disc damage on photos
  - SAP VF normal
- Baseline FDT obtained
- Mean follow-up 41 months

Medeiros FA, et al AJO 137:863-871, 2004

25

Other Important VF Studies

- Paczka (2001) - found FDT better overall performance in detecting damage than RNFL photographs
- Kondo (1998), Wu (2001) - In patients with SAP VFDs restricted to 1 hemifield, FDT has shown to be able to detect functional losses in the other hemifield
- Medeiros (2004) – functional defects in FDT predict future defects on SAP

26

Other Important VF Studies

- Kim (2007/AAO) – when SAP is normal, some patients with VFD detected by FDT showed decreased NFL thickness (OCT)
  - Provide evidence that coincident FDT & OCT abnormalities may be an early sign of glaucoma

27

Visual Field Testing for Specific Functions

- Short wavelength autoperimetry (SWAP)
  - Bistratified ganglion cell (9%) short-wavelength cones
- Frequency doubling technology (FDT)
  - Magnocellular ganglion cells
- Motion automated perimetry (MAP)
  - Magnocellular ganglion cells (3%)
- High pass resolution perimetry (HPRP)
  - Parvocellular ganglion cells

28

Closing Statements on Perimetry

- Advances in perimetry are continuing
  - Faster third generation algorithms reduce test time by 50%
- Customization for specific needs
  - Early detection / established glaucoma / screening
- Early VF loss is often selective, with specific types of axons disturbed
  - SWAP allows early recognition, HPRP follows progression
- SAP perimetry will continue to be preferred for established glaucoma with VFDs
  - Considerably improved methods of computer-assisted interpretations of serial VFs
- Screening methods will sacrifice sensitivity for specificity and ease of use to detect the half of glaucoma patients who have undiagnosed disease
  - Deployed in non-professional environments

29

Other Important VF Studies

- iPad App detects glaucoma visual field loss Johnson AmerJourOphthal November 2017
- Many cases of glaucoma are undetected particularly in developing nations
- Visual Field Easy iPad App (VFE) – was able to detect glaucoma with moderate loss (MD -6 to -12dB) and advanced loss (MD worse than -12dB)
  - It was not as effective at detecting early loss (MD less than -6dB)
- Conclusion – portable, quick, effective method to detect glaucomatous VFDs

30

Prognostic Factors in VF Progression

- Ophth 2013;120:512-519 Ernst, et al, in order
- Age (for all OAG)
- Disc hemorrhages (for NTG)
- Baseline VF loss
- Baseline IOP
- Exfoliation syndrome
- CCT
- Peri-papillary atrophy (for NTG)
- Proven previous VF progression

31

Glaucoma & the Brain

- Researchers view Glaucoma as a disease of the brain
  - Neurodegenerative disease
- Glaucoma shares common features with AD, Parkinson's and Lou Gehrig's diseases
- Offers potential for new treatments that promote nerve health, neurotrophic factors which can help at multiple places in the visual pathway
  - Neuroprotection – Ciliary neurotrophic factor (CNTF)
  - Neuroregeneration – increase axon regrowth
  - Neuroenhancement – improve support between dying RGC and surrounding cells in brain and retina

32

Scanning Computerized Ophthalmic Diagnostic Imaging 92133

- Unilateral or bilateral
- Applies to glaucoma or optic nerve evaluations
  - Heidelberg / Heidelberg Retinal Topography (HRT, Spectralis)
  - Carl Zeiss / Optical Coherence Tomography (GDX, Stratus, Cirrus)
  - Optovue / (RTVue, iVue)
  - Marco / Retinal Thickness Analyzer (RTA)
- Requires Interpretation & report
- Fee $42.24

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33

Ophthalmic Genetics

- Researchers have identified genes for OAG
  - TIGR/Myocilin = juvenile OAG
  - OPTN (optineurin) = Primary OAG (NTG)
    - Optineurin may provide neuroprotection to optic N
  - CYP1B1 = Congenital glaucoma
- Genetic testing will allow clinicians to determine if Pt is predisposed to or affected with specific type of glaucoma, even before symptoms appear
- OcuGene (InSite Vision/Alimeda) – simple, in office test, 99% accurate detection of TIGR (trabecular meshwork inducible glucocorticoid response gene)
  - Positives may be treated more aggressively, earlier

34

New Ideas in Glaucoma - Genetics

- Multiple genes & environmental factors interact in this heterogenous complex disorder
- Family history is one of the most important risk factors
- First degree relatives of affected patients demonstrate glaucoma 10 times more than general population
- 16 loci contributing susceptibility identified
  - Of these four genes isolated
  - Myocilin - more likely in early age of onset, family hx, elevated IOP
  - Optineurin
  - WDR36
  - NTF4

35

Low Tension Glaucoma

- Compromised ocular blood flow
- 50% have a cause / find it / fix it
  - Past hx transfusions, bleed, hypovolemic
  - Medications: B-blockers, digoxin, digitalis
  - MRI: orbits & brain
  - R/O all cardiovascular causes of LTG
    - CBC/anemias, CA doppler, TEE, sleep studies, coagulaopathies (PTT), overly fit (low BP)
- Treatment
  - Decrease IOP, avoid B blockers, start with PG, bromonidine, CAIs last resort
  - Ginko biloba 60mg/D: inc fluidity without affecting platelet aggregation

36

Characteristics of Glaucoma in Japanese Americans

- Pekmeezi M ArchOphthal 2009;127(2):167
- 1732 patients in Japanese-American clinic over a ten year period
  - 112 with glaucoma, 17% HTG, 70% NTG
- Proportion of patients with NTG was 4-fold higher than those with HTG

37

Do Superactivated Platelets Explain Disc Hemorrhages in Glaucoma?

- Disc Hemorrhage is a poor prognostic sign in ALL studies
- University of Chicago – SAPs associated with AD, TIA, corticle stroke
- Hemorrhages of optic nerve head and nailfold capillary bed characterize POAG
- Suggest that SAPs play a role in POAG
  - POAG patients display an elevated level of activated SAPs which are hyper coagulable

38

Do Superactivated Platelets Explain Disc Hemorrhages in Glaucoma?

- Platelets provide role in blood coagulation and circulate until they encounter thrombogenic elements and become activated, sometimes becoming superactivated
  - Phenotypically different and posses enhanced procoagulant and prothrombogenic activity
- Videocapillaroscopy to quantify vascular changes in the nailfold region demonstrated hemorrhages in 96.8% POAG, 92.3% LTG, secondary glaucoma 75%
  - 6 fold more hemorrhages than controls but different between all 3 forms of glaucoma (?)…new screening tool or ancillary

39

From the Literature

- 10% of blindness from glaucoma is from poor adherence to prescribed drugs
- DM, duration, fasting glucose, assoc w higher risk of POAG, and higher IOP – Di Zhao Ophthal 2015; 122
- Nocturnal hypotension predicted VF loss and worsening of defects – Charlson Ophthal 2014; 121
- Statin use significantly reduces risk of OAG in persons w hyperlipidemia – Stein Ophthal 2012; 119
- 3-5 times risk of acute angle closure with topiramate and buproprion
- GCC loss linked to decreased MPOD

40

Anti-Glaucoma Agents

- Non-Selective B-Adrenergic Antagonists
  - Timolol (Timoptic 0.25%, 0.50%, XE, Istalol/Ista Pharmaceuticals)
  - Levobunolol (Betagan 0.25%, 0.50%)
  - Metipranolol (Optipranolol 0.3%)
- Selective B-Adrenergic Antagonists
  - Betaxolol (Betoptic-S 0.25%, 0.50%)
  - Levobetaxolol (Betaxon)
  - Carteolol (Ocupress 1.0%)

41

Anti-Glaucoma Agents

- Prostaglandin Analogue
  - Latanoprost (Xalatan 0.005%) generic 3/2011
  - Bimatoprost (Lumigan 0.03%, Lumigan 0.01%*)
  - Travaprost (Travatan Z 0.004%) – No BAK
  - Tafluprost (Zioptan PF)
- The future – 7 PGA drugs currently being developed for sustained drug delivery systems
  - Nanoparticle size for injection

42

Latanoprost 0.005%

- Topical prostaglandin
- Indications: open angle glaucoma or ocular hypertension
- Side effects – hyperemia of conjunctiva, iris pigmentation/color change, lid erythema, eyelash growth
- Dosage: once daily at bedtime
- Advantages: monotherapy/compliance, favorable SE profile, longest track record, generic March 2011
- Available as ***Xalatan***
- ***Sustained release punctal plug coming soon!!***

43

Bimatoprost 0.03% & 0.01%**

- Topical prostaglandin
- Indications: open angle glaucoma or ocular hypertension
- Side effects – hyperemia of conjunctiva, iris pigmentation/color change, lid erythema, eyelash growth
- Dosage: once daily at bedtime
- Advantages: monotherapy/compliance, favorable SE profile with lower concentration but equal IOP lowering
  - Switch when having SE with other PGs or as first line PG
- Available as ***Lumigan, Lumigan 0.01%***
- ***Subconjunctival depo & external implant coming !!***

44

Bimatoprost 0.03% & 0.01%**

- ForSight Vision5 – Helios Insert
  - Polymer bimatoprost matrix in a soft compliant ring 26mm in diameter
  - Applied to ocular surface in office maintained under lids
  - Mean IOP reduction a t 6 months of 6.5mm
- Allergan – developing Bimatoprost SR
  - The amount of drug in implant is equivalent to one drop bimatoprost
  - Safer, less drug exposure, less side effects
  - Delivered intracamerally, prefilled single use applicator
  - Drug depleted in one year, implant gone in 2 years
  - POAG pts live 16 yrs / 32 injections / leave behind benign

45

Travoprost 0.004%

- Topical prostaglandin
- Indications: open angle glaucoma or ocular hypertension
- Side effects – hyperemia of conjunctiva, iris pigmentation/color change, lid erythema, eyelash growth
- Dosage: once daily at bedtime
- Advantages: monotherapy/compliance, favorable SE profile, long track record
- Available as ***Travatan-Z***
- ***Coming soon as medicated punctal plug***

46

Tafluprost 0.0015%

- Topical prostaglandin, first preservative-free preparation
- Indications: open angle glaucoma or ocular hypertension
- Supplied: 10 PF ampules per pouch, 3 pouches/box
- Side effects – same as other PGA
- Dosage: once daily at bedtime
- Storage: refrigeration necessary until pouch is opened, then once opened room temperature is fine
- Coming soon Tafluprost/timolol (Santen)
- Available as ***Zioptan / Merck***

47

Anti-Glaucoma Therapy

- Adrenergic Agonists
  - Dipivefrin (Propine 0.1%)
  - Epinephrine (Epinal,Eppy-N, Epifrin, Glaucon)
  - Apraclonidine (Iopidine 0.5%, 1.0%)
  - Brimonidine (Alphagan 0.2%, Alphagan P-0.1%, 0.15%) / Timolol (Combigan)
    - 41% less ocular allergy with Alphagan P vs Alphagan over 12 months
    - Only ophthalmic glaucoma drug without BAK
- Cholinergic
  - Pilocarpine (Pilocar 0.50% - 8.0%, Pilogel 4%)
  - Carbachol (Carbachol 0.75%, 1.5%, 2.25%, 3%)
  - Echothiophate Iodide (0.03%, 0.06%, 0.125%, 0.25%)

48

Antiglaucoma - CAI

- Topical
  - Dorzolamide (Trusopt)
  - Dorzolamide-Timolol (Cosopt/Cosopt PF)
  - Brinzolamide (Azopt)
- Oral
  - Acetazolamide (Diamox)
  - Methazolamide (Neptazane, MZM)
  - Dichlorphenamide (Darinide)

49

What is the Next BIG THING?

- Latanoprostene bunod 0.024% (Vyzulta) by Valeant/B&L-Nicox
  - Novel ***nitric oxide*** donating prostaglandin F2a analog
  - Decreases IOP 7.5mm - 9.1mm from baseline between weeks 2 &12 in phase 3 trials
  - Superior to timolol and latanoprost alone
  - Met endpoints both primary and secondary
  - Once daily dose
  - Minimal AEs – lash growth, hyperemia, ME, pain, iris pig
  - FDA approved January 2018
  - Supplied as 5cc bottle, average cost $375 bottle

50

What is the Next BIG THING?

- Netarsudil 0.02% (Rhopressa) by Aerie Pharma
- FIRST NEW MECHANISM OF ACTION in 20 years
- Triple action
- Inhibits rho kinase (ROCK) & norepinephrine transporter (NET), both biochemical targets for lowering IOP and reduces episcleral venous pressure (EVP) by 35%
  - ROCK inhibitors increase outflow via TM which is 80% of drainage from eye
  - NET inhibitors reduces production of aqueous
- Once daily dose

51

What is the Next BIG THING?

- Netarsudil 0.02% (Rhopressa) by Aerie Pharma
  - Downstream effect of small-G protein Rho
  - Potential to modify disease course by arresting fibrosis of TM
  - Suppresses activity of profibrotic proteins TGF-B2, CTGF on TM cells
  - Lowering EVP may help LTG or angle closure types
  - Theory – TM relies on aqueous percolation to supply nutrients, antioxidants
    - Diverting into uveoscleral outflow may not be good for TM long term health
- Mean IOP average reduction 6mm (?stand alone)

52

What is the Next BIG THING?

- Netarsudil 0.02% / latanoprost 0.05% (Roclatan) - Aerie
- Quadruple action – more impressive
  - Mean IOP 25.1 decrease to 16.5 on day 29
  - 2mm better than latanoprost alone
- Combination of triple action Rhopressa & Latanoprost
- Efficacy – superior to latanoprost
- Only glaucoma product covering full spectrum of currently known IOP lowering mechanisms of action
- Once daily dose
- SE - hyperemia

53

Glaucoma Market to Grow to $3B

- 2.3 Billion grows to 3 Billion by 2023
- Projected growth in seven major markets – US, France, Germany, Italy, Spain, UK and Japan is 2.4%
- Driven by first in class drugs
- Roclatan is forcast to achieve the highest sales expected to generate 262million in 2023
- Increase attributable to introduction of new drugs between 2013 and 2023 and overall increase in glaucoma prevalence
  - Mostly due to aging society in the US

54

Rho Kinase Inhibitors Future Thoughts

- Regulate cell morphology, proliferation, adhesion, motion, cytokinesis, apoptosis, neurite elongation, cytoskeletal changes to lower outflow resistance
- Increase blood flow by causing vascular smooth muscle relaxation leading to vasodilation
- Anti-tumor activity on surface
- Prevents axonal degeneration and promotes regeneration with neuroprotectant role at lamina demonstrated in eye
- Effect on conjunctival scarring after glaucoma surgery demonstrated could lead to new indication

55

Surgical Glaucoma Therapy

- Argon Laser Trabeculoplasty (ALT, LTP)
- Selective Laser Trabeculoplasty (SLT)
  - Q switched Nd:YAG selectively targets pigmented trabecular cells (increasing activity?)
  - Increases immune system by increasing monocytes & macrophages in TM
  - Selective because it does not cause appreciable damage to TM
  - 50 confluent applications to 180 degrees @0.06mJ
    - No blanching or bubble phase needed
  - Addresses greatest roadblock = compliance with medical therapy

56

Angle Laser Surgery

- Wise – 1970
- Mechanism – not known but shrinkage of trabecular ring with widening of spaces and decreased resistence to outflow is probable
- Particularly effective (90% controlled after one year)
  - Psuedo-exfoliation (PXF)
  - Pigment dispersion syndrome (PDS)
  - POAG
- Slowly and constantly loses effect
  - 55% at 5 years
  - 30% at 10 years
- Low complications with spike in IOP 30% (post-op)

57

Surgical Glaucoma Therapy

- Argon Laser Trabeculoplasty (ALT, LTP)
  - Q switched Nd:YAG selectively targets pigmented trabecular cells (increasing activity?)
  - Increases immune system by increasing monocytes & macrophages in TM
  - Causes appreciable damage to TM
  - 85 confluent applications to 180 degrees @0.06mJ
    - Blanching or bubble phase needed to assure proper treatment
  - Addresses greatest roadblock = compliance with medical therapy
  - Usually performed over 180 degrees of TM
    - Can be repeated to the other 180 degrees later if needed

58

Laser Surgery Before Medical Therapy?

- Glaucoma Laser Trial (GLT)
  - Multicenter/randomized study of safety and efficacy of laser first for newly diagnosed glaucoma
  - IOP better controlled at 2 years and 7 years
    - Less deterioration of cupping
    - Less deterioration of visual field
  - Limitations
    - Temporary effect
    - Better topical drugs with low side effects

59

New Approach to SLT?

- SLT available >12 years
- IOP decreases as well as PGA without medications
  - Daily medical adherence & tolerability issues
  - Targets pigment cells of TM without damage to TM structures
  - Can be safely effectively repeated
- Standard therapy – 70 to 80 spots over 360 degrees
  - Starting at 0.5mJ titrating up to bubble
- Annual retreatment – 40 to 50 spots over 360 degrees
  - Starting at 0.4mJ, titrating up to bubble

60

New Approach to SLT?

- Results
  - 16% on topical Rxs in follow up vs 53% with SLT and 62% with ALT
- Conclusion
  - Annual SLT with lower power better then as needed SLT or ALT in reducing need for medications and time to medications in newly diagnosed glaucoma or ocular hypertension

61

Methods of Lowering IOP with MIGS

- Aqueous humor production- Endocyclophotocoagulation (ECP) / Endo Optics Beaver Visitec
- Schlemm's canal – Trabectome / Neomedix; iStent / Glaukos
- Suprachoroidal space – CyPass Transcend Supra, iStent Supra
- Subconjunctival space – XEN / Aquesys, InnFocus MicroShunt, MIDI Arrow Glaucoma Device / Innova

62

Endocyclophotocoagulation -ECP

- Reduces production of aqueous fluid by utilizing laser energy to treat the ciliary processes
  - Disables some of the ciliary epithelium
    - Works on inflow production of aqueous
  - Ideal procedure to combine with cataract surgery
    - Endoscope can be inserted through same incision for cataract surgery
    - Expect 20-30% drop in IOP
    - Drop in IOP is not immediate like filtering surgery but improves with post operative decrease in inflammation
    - Requires viscoelastics out of the bag to move iris for probe

63

Trans-scleral Cyclophotocoagulation

- Historic methods of ciliary body destruction
  - Cyclocryopexy, etc
  - Many complications including cataract, pain, phthsis
  - Simple and in-office procedures
- Ab interno or Ab externo
- Non-contact or contact Nd:YAG, or Nd:Diode
- New Method – micropulsed laser uses 0.5us doses, rapidly alternated with 1.1us rest over 100 sec rather than for 2 sec continuously as previous
  - Can use earlier

64

Addressing Outflow - Goniotomy

- Kahook double Blade (New World Medical) – single use instrument excises a strip of trabecular meshwork
- Trab 360 (Site Sciences) – completes a 360 degree cut in TM using a filament inside schlemm's canal
- Trabectome (NeoMedics) – targets meshwork, ablating, I&A, electrocautery
- iTrack250A Microcatheter (Ellex) – enlarge schlemm's canal then tear it open by removing catheter

65

Trabectome (NeoMedix)

- Goniotomy
- One use disposable device
- Bipolar electro-surgical pulse 550KHz/0.1w incr
- Simultaneous irrigation & aspiration
- Ablation of TM and unroofing of schlemm's canal and juxtacanalicular tissue
- Average IOP decreases from 24mm to 15mm @60m
- Topical Rxs decrease from 3 to 1 @60m
- Advantage – easy, outpatient, option to delay trabeculectomy, less side effects

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66

Glaukos iStent Trabecular Bypass

- Smallest medical device approved by FDA
  - 1mm long, 0.33mm height, snorkle 0.25mm x 120um, 60ug
  - Nonferromagnetic titanium single use, sterile inserter
- Approved for mild-moderate glaucoma
- Placed during cataract surgery
- Spares tissues damaged by traditional procedures
- Contraindicated in NVG, PAS, primary or secondary angle closure glaucoma, angle abnormalities
- Adverse events – corneal edema, loss of BVA>1 line, PCO, stent obstruction

67

Glaukos iStent Trabecular Bypass - Next

- iStent Inject – second iteration
  - 0.4mm single piece mushroom shaped titanium stent with fenestrations placed ab interno with preloaded inserter allowing multiple placements without leaving the eye
- iStent Supra – targets drainage through uveoscleral outflow
  - Advantage is larger surface area and negative pressure gradient
  - 4mm titanium stent placed into the supraciliary space
  - Results – lower IOP by 20% and reduction of at least 1 medication

68

Schlemm Canal Scaffold Implant

- Hydrus / Invantis
  - Alone or in combination with cataract surgery
    - 1.5 mm incision
  - Mild-moderate glaucoma
  - 8 mm long device, flexible biocompatible nitinol
  - Enters canal, resides in canal, provides tension on inner wall
- Results in significant, durable decreases in IOP and medication use
  - Best results in combined surgery – 16.6mm/0.1 Rxs @24m
  - Alone results – 18.6mm / 0.5 Rxs @24m
    - 70% less use of medications

69

Schlemm Canal Scaffold Implant

- Hydrus / Invantis
  - Received FDA approval for treatment of mild to moderate open angle glaucoma in conjunction with cataract surgery
  - MIGS device – multimodal
    - Creates large opening in trabecular meshwork
    - Dilates and scaffolds the conventional pathway through which aqueous exits the eye
- Horizon Trial – N = 556
  - 77.2% saw greater than 20% reduction in IOP at 24 mos
  - Mean IOP reduction of 9.4 mmHg
  - Over 4000 procedures worldwide, many over 5 years
  - Launch end of 2018

70

Schlemm Canal Scaffold Implant

- Hydrus / Invantis
  - Gives 90 degrees coverage of canal
  - Extending over multiple collector channels
  - Eliminates need for precise placement
  - Eliminates need for implantation of multiple devices
- Key findings in trials
  - 77% of treated patients had IOP reduction of 20% or more
    - Largest treatment effect for any MIGs trial at 24 months
  - 43% difference between treated patients and control group
    - Largest difference in IOP reduction reported in a MIGs trial at 24m
  - 78% of treated group remained medication-free at 2 years
    - Largest number for medication elimination of any MIGS trial

71

CyPass Micro-Stent / Alcon

- Stent the supraciliary space and augments uveoscleral outflow (like iStent Supra)
- Targets suprachoroidal outflow in redirecting aqueous outflow
- Fenestraed micro-stent 6.35mm long and 510u in diameter
- Polyimide material
- Ab interno insertion is easier than other stents
- Results – reduction in IOP by 33% and 50% decrease number of medications at one year
- Removes need for one IOP lowering drug, maybe more

72

CyPass Micro-Stent / Alcon

- Voluntary withdrawal of all versions of CyPass from global market on August 29, 2018
- Based on safety data from Compass-XT study which found statistically significant difference in endothelial cell loss at 5 years after surgery
  - More common when device is not as deep into angle
  - Correlates to number of rings visible on stem
- Intend to work with regulators to relabel the device for reintroduction
- The FDA did not mandate this, Alcon was proactive with safety in mind

73

XEN Gel Stent - Allergan

- Gel stent is preloaded in a disposable injector with a 27-gauge needle and delivered into the non-dissected Tenon space creating a connection from the anterior chamber to the subconjunctival space (Bypasses Schlemm's canal)
- FDA approved w efficacy similar to trab, removing 2 drugs from regimen, ***requires bleb management***
- Gel that hydrates on insertion
  - 3lum Ab interno collagen pre-loaded implant of cross linked porcine en sizes: 140u, 63u, 45u
  - 1mm in AC / 3mm in sclera / 2mm in subconj space
- 40% reduction in IOP at 36 months, 74% reduction in Rx
- Adverse events – hyphema, encapsulation of bleb requiring needling, requires MMC

74

InnFocus (InnFocus, Miami)

- Small stent is creating a connection from the anterior chamber to the subconjunctival space
  - Bypasses Schlemm's canal entirely
- Polystyrene-block isobutylene
- Phase 3 in US; Europe for mild-moderate glaucoma, & advanced w efficacy similar to trab
- Ab externo approach with conjunctival dissection of scleral flap, creates diffuse bleb
  - Lowers IOP 10mm
- More appropriate for advanced disease requiring lower IOP
- Adverse events – hyphema, bleb complications, hypotony

75

ABiC - 360 Degree Trabeculotomy

- Ab interno canaloplasty (ABiC)
- One use disposable device
- Alone or combined with cataract surgery
- Canaloplasty = 44% IOP reduction
- Tears and unroofing of schlemm's canal and juxtacanalicular tissue
- Average IOP decreases from 24.4mm to 13.7mm
- Topical Rxs decrease from 1.5 to 0.2 @12m
- Technically complex and long to perform

JAM

76

360 Degree Trabeculotomy

- iTrack catheter 250u
- Initial use was for childhood glaucoma with poor prognosis, Failed goniotomy, infantile glaucoma after cataract surgery, infantile glaucoma associated with ocular or systemic conditions, progressive congenital glaucoma and corneal clouding
- Outcomes 87-92% successful
- Trabeculotomy codes already exist
- Formerly iScience Surgical
- Now iScience Interventional, Menlo Park CA

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77

Cataract Surgery in Glaucoma Patients

- Combined surgery indications
  - Glaucoma treatment failing with topicals
  - Significant disc changes and visual field damage
  - Transient elevations of IOP associated with surgery or topical steroids may cause further damage
  - Cataract surgeons should spare conjunctiva superiorly for future placement of filters or implants
  - Benefit of definitive surgical solution to both problems with one operation
- Premium IOLs – historically shy away from lenses that decrease contrast sensitivity (POAG causes this first)
  - Toric IOLs, EDOF IOLs, Accommodating IOLs are OK

78

Neuroprotectants

- Memantine (Nameda) –blocks Na, K channels, retards apoptosis
- Brimonidine(?)
- Ciliary neurotrophic factor – CNTF phase I as implant
- BDNF – inhibits programmed cell death
- Erythropoetin- EPO
- Future is neuroprotection to improve environment and
  - neurodegeneration with stem cells
  - Neuroenhancement supports injured RGCs before they die
  - Immunobiology with T cell based vaccination

79

Nanosensor IOL

- Fraunhofer Institute in Germany
  - Microelectric Circuits and Systems IMS
- Implant sensor for continuous IOP monitoring
- Integrated a 2.5 by 2.6 millimeter sensor in an IOL
- The top and bottom of the sensor are electrodes
  - The top electrode is flexible, bottom of the sensor is rigid
  - When the intraocular pressure increases, the top electrode is pushed in, reducing the distance between the top and bottom of the sensor and thus increasing the capacitance
- Implant sends the pressure data to a reader that is fitted into the frame of a pair of spectacles
- An antenna in the spectacle frame supplies the sensor with the required energy via an electromagnetic field
- Currently undergoing clinical trials
- Could come available in two to three years time

80

Nanosensors IOP

- MIT Technology Review
- A pressure sensor to measure glaucoma IOP
- Tiny microchip implanted subretinal
- The sensor is designed to measure IOP
  - wirelessly transmit the data to computer
- One of the major obstacles in creating this type of device is designing a tiny but highly functional chip that uses very little power
  - Sensor runs on nanowatts rather than on microwatts
- The researchers began testing the implant in animals last December

81

Glaucoma's Origins – Immune System?

- Investigators at Massachusetts Institute of Technology speculate that glaucoma be filed under autoimmune disease
- Used mice deficient in T cells, B cells, or both and a process called adoptive cell transfer
- Uncovered "compelling evidence that glaucomatous neurodegeneration mediated in part by T cells that are pre-sensitized by exposure to commensal microflora"
- In mice with glaucomatous damage, T cells infiltrated retina when IOP rose
- Once blood-retina barrier breached, they target heat shock proteins
  - Help cells respond to stress or injury
  - T cells attack the protein because they perceive them as a threat due to poor exposure to bacterial heat shck proteins
- Found human patients with glaucoma have 5 times the normal level of T cells specific to heat shock proteins
- First to report the unexpected link between the sequential roles of elevated IOP, intact commensal bio flora and activation of T cell responses in pathogenesis of glaucoma

82

Thank you

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Excellence in Optometric Education

83