Current Topics in Glaucoma

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Update and Insight on New Drug Delivery Systems

Compliance, Persistence, and Adherence

- Compliance: The act of conforming, acquiescing, or yielding; cooperation or obedience
- Adherence: A measure of the degree to which a patient follows prescribed instructions during a defined time period.
    - E.g. Timolol BID over 30 days; patient uses 20 drops; adherence is 33%
    - Allows the patient to have lapses in drug use and summarizes the percent of days that the patient uses the drug
- Persistence: A metric that evaluates the time until a patient first discontinues the use of a medication.
    - E.g. patient is prescribed PGA on January 1 and fills 2 prescriptions, but doesn't fill on in March, but restarts in April is persistent for 2 months.
    - Measures the time to discontinuation.
- White Coat Adherence: Patient adherence rises sharply 1 week before examination and then declines rapidly following

Variability by Drug Class and Therapy

- PGAs have higher degree of persistence and adherence
- Nearly half of monotherapy patients had stopped using medications at 6 months
- Less adherence and persistence with polytherapy
    - A second drug leads to reduced filling of first-prescribed medication.

Barriers to Adherence and Persistence

- Cost
- Tolerability
- Dosing schedule
- Denial
- Lack of education about disease
- Forgetfulness
- Travel
- Schedule

Rho and Rho-associated protein kinases (ROCK)

- The Rho family consists of three small guanosine triphosphate (GTP)-binding proteins (RhoA, RhoB, RhoC), which regulate aspects of cell shape, motility, proliferation, and apoptosis throughout the body
- ROCKs are serine/threonine kinases that regulate smooth muscle contraction, specifically in the TM

- ROCK1 and ROCK2 tend to be expressed in the majority of tissues, including human TM and ciliary muscle cells
- ROCKs appear to have several actin cytoskeletal-related targets that directly affect the contractile properties of TM outflow tissue
    - Loss of ROCK function has previously been associated with micromechanical relaxation of cells and disassembly of stress fibers and focal adhesion complexes enhancing aqueous outflow
- Multiple studies have indicated that ROCK and Rho GTPase inhibitors can increase aqueous humor drainage in TM tissue, leading to a reduction in IOP
- ROCK inhibitors induce reversible modifications to cell morphology and cell interactions in the eye that facilitate greater outflow of aqueous humor and, ultimately, result in a lower IOP.
- ROCK inhibitors exhibit a widening of the extracellular spaces and juxtacanalicular tissue
    - morphological changes within 30 minutes of administration and lasting up to 12 hours
- ROCK inhibitors may have uses in glaucoma management other than lowering IOP. Animal studies have demonstrated increased ocular blood flow as well as potential neuroprotective effects, and ROCK inhibitors may also have the potential to reduce postoperative scarring during glaucoma-filtering surgery
- Topical Rho kinase inhibitor AR-12286 demonstrated a dose-related ocular hypotensive efficacy in patients with elevated IOP. Three concentrations of AR-12286 produced statistically and clinically significant reductions in mean IOP relative to diurnally adjusted baseline, with peak effects occurring 2 to 4 hours after acute or chronic dosing.
    - The overall hypotensive efficacy was dose dependent, with the 0.25% concentration producing the largest reductions in mean IOP (6.8 mm Hg) and the longest duration of effect, up to 24 hours after a once-daily dose. Twice-daily dosing provided greater ocular hypotensive efficacy throughout the day than once-daily dosing in the morning or the evening
- Rhopressa™ is a novel triple-action eye drop that, if approved, would become the only once-daily product available that specifically targets the trabecular meshwork, the eye's primary fluid drain and the diseased tissue responsible for elevated IOP in glaucoma. Preclinical results have demonstrated that Rhopressa™ also lowers episcleral venous pressure, which contributes approximately half of IOP in healthy subjects. Further, Rhopressa™ provides an additional mechanism that reduces fluid production in the eye and therefore lowers IOP. Biochemically, Rhopressa™ is known to inhibit both Rho Kinase (ROCK) and norepinephrine transporter
    - ROCKET-1 study (AR-13324 Ophthalmic Solution, 0.02%)-Rhopressa™
        - Did not meet the primary efficacy endpoint of demonstrating noninferiority of IOP lowering for once-daily Rhopressa compared to twice-daily timolol
            - Rhopressa did not meet its primary efficacy endpoint based upon IOP measurements at the end of weeks 2 and 6 and day 90
            - Rhopressa showed slight loss of efficacy at week 6 and day 90 (approximately 20%).
            - The primary adverse event was hyperemia, which was experienced by approximately 35% of the Rhopressa patients, of which 80% was reported as mild.
- K-115 clinical trial

    - Mean IOP reduction of up to 4.3 mmHg for the highest concentration of treatment was observed 1–2 hours after instillation. More than half of participants treated with K-115 showed slight to mild conjunctival hyperemia
- Rho Kinase (ROCK) inhibitors may enhance TM outflow of aqueous as well as provide additional benefits. Hyperemia is the most commonly reported adverse effect. However, approval is still elusive as IOP efficacy hasn't been adequately proven.

Wouldn't it be great to have sustained release medications? Sustained-release options

- Currently, there are no FDA-approved and clinically available sustained-release drug delivery systems for glaucoma.
- Allergan is currently performing phase 3 clinical trials on its bimatoprost sustained-release implant (bimatoprost SR), which is an intracameral depot implant injected into the anterior chamber.[1]
    - Phase 2 trials of the implant showed a mean IOP reduction from baseline of 7.2 to 9.5 mm Hg in 75 eyes 4 months after the injection. The fellow eyes received once-daily topical bimatoprost 0.03% and experienced an IOP reduction of 8.4 mm Hg.
    - The implant lowered IOP in 92% of patients at 4 months and 71% at 6 months.
    - There were no serious adverse ocular events, and the most common adverse events were related to the injection procedure.

1. Allergan. Positive phase I/II interim data of bimatoprost sustained-release implant for IOP therapy in glaucoma. November 16, 2015. http://bit.ly/1QhSGfr. Accessed December 14, 2015.

- Another depot implant that is injected intracamerally and targets the anterior chamber is ENV515 by Envisia Therpeutics. ENV515 is a biodegradable polymer drug delivery system that uses an extended-release formulation of travoprost. A phase 2a open-label, 28-day dose-ranging study of 21 patients yielded 6.7 mm Hg or 28% IOP lowering at day 25 in one group, which was comparable to once-daily Travatan Z (travoprost ophthalmic solution; Alcon) dosing in the fellow eye. Envisia is planning to advance to a 12-month study to evaluate the long-term IOP lowering of ENV515.[2]

2. Envisia Therapeutics. Envisia Therapeutics' lead product candidate, ENV515 (travoprost XR), achieves primary efficacy endpoint in phase 2a glaucoma clinical trial. October 6, 2015. http://prn.to/1NljZBr. Accessed December 14, 2015.

- GrayBug is developing a microparticle controlled-release drug delivery system for the treatment of age-related macular degeneration (AMD) and glaucoma. GrayBug is developing compounds with both IOP-lowering activity and neuroprotective benefits. In animal models, the company has achieved IOP reduction lasting months with subconjunctival administration of the depot drug using two generic medications.
- Icon Bioscience combines drugs with a carrier platform called Verisome into a true liquid injection that can be placed in the posterior or anterior segment. A glaucoma product is in the preclinical phase.

PLATFORMS DELIVERED OUTSIDE THE EYE

- The Helios (ForSight Vision5) is a bimatoprost-laden polymer-matrix insert embedded in a compliant ring. The ring is positioned under the upper and lower eyelids and rests on the conjunctiva. It is visible only at the caruncle once it is in place. The ring is designed to be replaced by a physician every 6 months.
    - In a phase 2 randomized, double-masked controlled study, the Helios with bimatoprost and artificial tears was compared to a placebo insert and timolol 0.5% BID. The bimatoprost insert lowered IOP, but less than did topical timolol 0.5% dosed twice daily in eyes with an unmedicated insert.[3]
    - Ninety percent of subjects who tried the implant were comfortable, and those who rejected it typically did so within a few days of its placement. A limited sample size of 50 to 60 patients in each arm may have affected the analysis. A much larger phase 3 trial is therefore planned.

3. Brandt JD, Sall K, DuBiner HB, et al. 6-month IOP-reduction with a single dose of a novel topical bimatroprost ocular insert: a phase 2 randomized, double-masked, controlled study. Paper presented at the: AAO Annual Meeting; November 17, 2015; Las Vegas, NV

- Ocular Therapeutix and Mati Therapeutics are performing clinical trials relating to punctal plug drug delivery.
    - OTX-TP releases travoprost and is visible via fluorescence.
    - May require flushing the canaliculus with saline or other maneuvers if removal is needed.
    - Retention of the OTX-TP device was 91% at 60 days and 48% at 90 days.
- Mati Therapeutics device, L-PPDS (latanoprost-punctal plug delivery system), is a drug-eluting punctal plug. L-PPDS releases latanoprost and is grossly visible. As a superficial punctal plug, it can be pulled out relatively easily.

Great Things About Sustained Delivery

- Compliance is greatly enhanced
- Fewer issues for patients

Not So Great Things About Sustained Delivery

- Injectable meds and implants- if med doesn't work topically or has adverse effects, drop is stopped; can't easily stop implantable devices. Implants can theoretically block parts of the angle
- Complications with invasive options
    - Endophthalmitis
- Patients still have to verify if plug or ring is still in place
    - May be challenging for some
- Limitations- how many drugs can you load into a ring or put in the anterior chamber? Patients only have 2 puncta per eye- may still need topical therapy as well
- Drugs may work better in pulsatile form and not so well in constant delivery
- PGAs less effective at BID dosing- receptor supersaturation and desensitization
    - Downtime between drops prevents desensitization

- SR products seem less effective than drops
- Will insurance pay for it just to increase compliance?

Issues in OCT Imaging

What to look for when interpreting OCT scans

- Quality score
    - Want signal strength or quality index to meet manufacturer's recommendations
        - Cirrus – 7 or above
        - Optovue – 30 or above
        - Heidelberg – 15 or above
- Illumination
- Focus clarity
- Image centered
- Any signs of eye movement
- Segmentation accuracy
- B Scan centration

Issues in Imaging

- Media opacity or irregular corneal surface can cause suboptimal OCT image quality that also affects the RNFL or macular thickness measurements. Coexisting posterior segment pathologies including epiretinal membrane and retinoschisis may cause overestimation of RNFL or macular thickness, leading to false-negative results. Additionally, clinicians should also consider age-related decline of RNFL and macular thickness when assessing glaucoma progression.
- Different SD-OCT machines utilize different methods of image registration to maximize consistency between measurements. Spectralis OCT utilizes eye-tracking technology, which identifies retinal structures as reference points. The machine in subsequent scans recognizes these reference points and places the scan circle in the same location as the baseline scan.
- The RTVue-100 registers blood vessels, which subsequent scans can use to place the scan circle at the same point. The Cirrus HD-OCT and Topcon 3D-OCT 2000 serially register pixels of the RNFL thickness maps over a 6×6 mm^2 peripapillary area. On each visit, they automatically place the scan circle at the same location post-scan acquisition and compares pixels of subsequent scans against baseline scans to identify change.
- SD-OCT machines provide trend-based analysis of average and/or sector RNFL thickness. However, because of the localized nature of glaucoma progression, comparison of multiple RNFL thickness profiles obtained over time should be more sensitive in detecting subtle RNFL thickness changes.

Sources of Misinterpretation

- Normative Database
    - SD-OCT measurements are compared against an age-matched normative database. The normative database for the Cirrus SD-OCT consisted on 284 healthy individuals with an age range between 18 and 84 years (mean of 46.5 years). Ethnically, 43% were Caucasian, 24% were Asians, 18% were African American, 12% were Hispanic,

1% were Indian, and 6% were of mixed ethnicity. The refractive error ranged from -12.00 D to +8.00 D. Due to this relatively small normative database and wide variation of distribution of RNFL, many results obtained by SD-OCT may be flagged as abnormal statistically in patients who are not represented in the database and thus not necessarily representing real disease. Clinicians should use caution to avoid over-treating "red disease" in these situations

- Signal Quality
    - When assessing the adequacy of a scan, the signal strength should always be noted. The signal strength is defined as the averaged intensity value of the signal pixels in the OCT image. The best quality scans have signal strength greater than manufacturers' recommendations. Artificially defocusing an image scan by +2 diopters results in 10 μm thinning of the RNFL.
- Blink/Saccades
    - An SD-OCT RNFL scan consists of multiple single A-scans side by side to represent a B-scan cube. With eye movement or blinking, these scans do not align correctly which can lead to an erroneous RNFL thickness measurement, which may be misinterpreted as progressive thinning. The new SD-OCT versions have a built-in eye tracking function which can help compensate for eye movement by relying on blood vessel registration or iris tracking. Using the eye tracker significantly improves the reproducibility of RNFL measurements
- Segmentation Errors
    - It is important to look at the segmentation lines produced by any SD-OCT machine's software algorithm to ensure that they are appropriately placed. Lines should not come together (go to zero). Occasionally, one will find that the segmentation lines are misplaced along the retina leading to errors in the calculation of RNFL thickness. These segmentation errors are more common in the presence of poor signal strength, tilted discs, staphylomas, large peripapillary atrophy, epiretinal membranes, and posterior vitreous detachments.
- Media Opacities
    - The en face scanning laser ophthalmoscope (SLO) image should be examined to ensure the absence of media opacity, such as a posterior vitreous detachment (PVD), within the circumpapipillary scan area. Areas in which data is missing due to an opacity are represented in black on the en face SLO image. In such a case, the overlying PVD can lead to a falsely thin RNFL measurement in the underlying area. Additionally, cataracts can affect RNFL thickness measurements. This effect is most pronounced in cortical cataracts, followed by posterior subcapsular cataracts. Nuclear cataracts were not found to affect signal strength or RNFL thickness measurements
- Axial Length
    - Axial length has been shown to influence SD-OCT measurements of both RNFL thickness and ONH parameters due to axial-length induced ocular magnification. The longer the eye, the thinner the RNFL

Red vs. Green Disease in OCT

- Issue of 'red disease'
    - Normal patient falls outside of normative data base
        - Over diagnoses glaucoma

    - Green Disease
        - Abnormal patient falls within the normative data base
            - Underdiagnoses glaucoma
- Understanding imaging interpretation and role in glaucoma diagnosis

Judging Glaucomatous Progression

- Progression may be measured by
    - Functional change as indicated by visual field deterioration
    - Structural change in the optic disc or retinal nerve fiber layer
- Progression can be categorized as event analysis or trend analysis
    - Event analysis- compares baseline to most recent data; change as dictated by criteria has occurred or not
    - Trend analysis looks at the significance of rate of change over time.
        - Identifies progression by looking at patient behavior over time.
        - Uses all data points and a linear regression formula
        - Main Weakness- progression is not necessarily linear
- Glaucoma progression rate is the most important determinant of therapy and future visual impairment
- Past progression rate is the most influential determiner of future progression rate
- Measuring rate of progression is difficult as it is hard to differentiate true change from variation in testing.

Risk Factors for Progression:

- IOP level
    - The most significant modifiable risk factor for glaucoma development and progression
- IOP fluctuation
    - Possibly indicates changing perfusion pressure and decreased autoregulatory ability
    - This was identified in the AGIS study, but faulty reasoning has led the glaucoma community to reject this as an independent risk factor
- Exfoliation
    - Higher IOP, worse disease, more difficult to control, noted in numerous studies in association with progression
- Central Corneal Thickness (CCT)
    - OHTS and many others point out that thin cornea a risk factor
- Disc hemorrhages
    - Patients with normal tension glaucoma, primary open angle glaucoma, ocular hypertension
        - Anemia, posterior vitreous detachment, vascular occlusion can cause hemorrhages of the disc that are mistaken for glaucomatous disc hemorrhages
    - Ischemic or mechanical
    - Probable infarction of the blood supply to the ONH
    - Inferior, inferior temporal, superior, superior temporal regions of the disc most susceptible and account for virtually all true disc hemorrhages

        - Hemorrhages at other areas of the disc (nasal and temporal) tend to not be associated with glaucoma
        - Typically occurs where notches occur
        - Resides in the retinal nerve fiber layer
            - Not in the cup
        - Small and contiguous with the neuroretinal rim
        - Can be recurrent and, if it recurs, it typically is in the same place on the disc each time
        - Precedes notching, NFL defect, field loss. Perhaps the earliest change in glaucoma (if it happens)
        - More common in patients with large IOP variations
        - Meaning is unclear – possibly indicates poor control of IOP?
        - Disc hemorrhages do not constitute a diagnosis of glaucoma nor a progression or conversion to glaucoma or an endpoint for any major glaucoma
- Time
    - Glaucoma is by nature a progressive disease and treatment likely only slows the progression
    - Given enough time, most will demonstrate progression and this is not a sign of treatment failure
- Ocular Perfusion Pressure (OPP)
    - The difference between systemic blood pressure and intraocular pressure.
        - A measure of retinal and optic nerve perfusion
    - Systolic Perfusion Pressure (SPP)
        - SPP = Systolic Blood Pressure – IOP
    - Diastolic Perfusion Pressure (DPP)
        - DPP = Diastolic Blood Pressure – IOP
    - Mean Perfusion Pressure (MPP)
        - MPP = Mean arterial pressure – IOP
            - Mean Arterial Pressure = 2/3 DBP + 1/3 SBP
    - Lower OPP strongly associated with prevalence of POAG
    - Six-fold excess risk of having glaucomatous optic nerve damage in persons with lowest category of OPP

Patient Compliance

- Nearly 50% of patients show non-continuous use by 6 months after start of therapy
- Communication Skills and Information Exchange
    - How well the Doctor communicates the importance of compliance
- Choice of Medications and the treatment regimen
    - Managing side effects
    - Impact the diagnosis and medication has on one's quality of life
- Situational and Environmental factors
    - Other diseases
    - Life events
    - Social support
- Assorted other factors
    - Cost

- Insurance and formulary issues
- Physical barriers
    - Drop instillation difficulties due to arthritis

Risk Factors for Progression: Summarizing What the Major Studies Tell Us

- Disc hemorrhage (NTGS, OHTS, EMGT)
    - NTGS, EMGT saw no difference with IOP reduction
- Fluctuation of IOP (AGIS)
    - Technically reported, but not accurate or accepted
- Thin cornea (EMGT, OHTS)
- Higher baseline IOP (EMGT, OHTS, AGIS)
    - Not CNTGS
- Exfoliation (EMGT)
- Cardiovascular disease (EMGT, NTGS)
- Lower OPP (EMGT)
- Older age (EMGT, AGIS)
    - *not* CNTGS

Clinical Pearl: In most patients, there will be a change in structure as the first sign of progression and in others the visual field will change first. Those that show a combined structural-functional change usually are being followed at intervals that are too far apart.

Combining Functional and Structural Measurement for Glaucoma Diagnosis and Determining Progression

- In reality, there are patients that show structural changes first in glaucoma (likely the majority) and others that show functional changes first
- The combination of a functional test (visual field analysis) and a structural measurement (disc photograph or imaging device) allows for most accurate diagnosis as one alone is likely not enough.
- Importance and limitations of clinical assessment
    - Wide diversity of normal appearance
    - Potential overlap of non-glaucomatous and glaucomatous
- Clinical application of imaging
    - Diagnosis
        - Normal vs. abnormal
    - Determination of progression or stability

Limitations of Functional Measurement

- Reliability and reproducibility biggest limiting factor
    - In the OHTS, an attempt was made to identify the occurrence of normal visual field test results following 2 vs. 3 consecutive, abnormal, reliable test results in the OHTS study
        - A VF endpoint confirmed by 3 consecutive abnormal, reliable VF test results appears to have greater specificity and sensitivity than either 1 or 2 consecutive abnormal, reliable VF test results.

        - However, some eyes whose VF POAG endpoint was confirmed by 3 consecutive abnormal, reliable VF test results nonetheless had 1 or more normal tests on follow-up.
    - AGIS: In patients with advanced glaucoma, a single confirmatory test 6 months after a VF worsening indicates with at least 72% probability a persistent defect when the worsening is defined by at least 2 decibels of MD.
        - When the number of confirmatory tests is increased from 1 to 2, the percentage of eyes that show a persistent defect increases from 72% to 84%.

- Ability to understand test
- Patient physical limitations to sit through long tests
- Significant damage must occur prior to measurable functional loss
- Subjective interpretation of results

Limitations of Structural Measurement
- Artifact in acquisition
    - motion, media, placement of measurement, operator skill
- Anatomy not consistent with normative database to which patient is being compared
    - severely tilted discs, extreme variations in disc size, high myopia
    - Very early damage
        - acquired change has occurred but does not exceed the range of normal values
    - Advanced damage
        - little value obtained from images from clearly end extensively abnormal optic nerves and retinal nerve fiber layer
        - dynamic range of device is exceeded, abnormality is clear, values too low to be able to determine progression
- Subjective interpretation of results

When to do each and when to repeat?
- Visual fields more often due to long term fluctuation and learning curve
- Annually if stable, more often if unstable
- Photographs and imaging at time of initial diagnosis and then annually thereafter

When not to do each and when not to repeat?
- Poor initial quality
- Photographs and imaging not helpful in very advanced disease
    - No information to be gained
    - Can't judge progression in a 95% cupped nerve

Functional Testing: Visual Fields

New Technologies for Measuring Progression: Visual Field Guided Progression Analysis (GPA)
- *Guided Progression Analysis*

- Used with Humphrey HFA II-i perimeter
- Uses algorithm developed for Early Manifest Glaucoma Trial
- Designed to help identify clinically significant progression of visual field loss in patients with glaucoma
- Highlights changes from selected baseline examinations that are larger than typical clinical variability in patients with similar degrees of glaucoma.
- Identifies consistent and repeated patterns of loss
- Corrects for ocular media effects
- Analysis based upon detailed empirical knowledge of variability found at all stages of glaucomatous visual field loss
- Can be used on full threshold (baseline only), SITA Standard, and SITA Fast strategies
- Visual fields that repeatedly and consistently show changes exceeding what is known to represent typical variability are identified a s having "possible" or "likely" progression

Structural Testing: Photographs and Imaging Devices

- Using photographs to judge progression can be difficult with a steep learning curve. Subject to errors based upon observer as well as artifacts of camera and equipment
- Newer approaches use imaging devices and statistical analyses
    - Two possible reasons for change on imaging devices
        - Error in acquisition, error in image registration, poor image quality/ signal strength, cataract, inherent variability in measurement
        - True biological change
            - Differentiating one from the other is difficult
- Guided Progression Analysis now available for OCT; RNFL and soon GCC

When is surgery wrong for the patient?

- When the risk of surgery is greater than its expected benefit.
- When it is more dangerous to undergo a surgical procedure than to continue on the same medical treatment.
- When you would not recommend the same intervention to your family members
    - Establishing the treatment course
        - Is the disc or field status stable or worse?
        - If progression has occurred, over what time period?
        - What is the rate of change?
        - What is the risk of visual disability in the patient's lifetime?
        - Is the patient aware of either decreased central visual acuity or peripheral visual field loss?
            - Classic question: Is it the cataract or the glaucoma or the age related macular degeneration?

When is filtering surgery wrong?

- The blind painful eye
    - Treatment is aimed to achieve a comfortable eye (neovascular glaucoma)
    - Time honored concept – no invasive surgery in a blind eye
        - Alcohol/ chlorpromazine injection, cyclodestruction

- Rare reports of sympathetic ophthalmia after cyclodestructive procedures (cyclophotocoagulation)
- Meds: IOP reduction, steroids, atropine
- If pain cannot be controlled – enucleation or evisceration are excellent options

Surgical risks

- Intraoperative suprachoroidal hemorrhage ("explusive hemorrhage")
  - Risks – elderly, hypertensive, prior vitrectomy, aphakia, very high preoperative IOP
  - About 1:1500 to 2000 overall
- Postoperative endophthalmitis
  - About 1:1500 to 1:2000 eyes in USA
- Ptosis
  - Uncommon, probably less than 2%
- Trabeculectomy
  - Immediate postoperative period
    - Hypotony – flat anterior chamber, acute cataract, angle closure, choroidal effusion
    - "Wipe out" or "snuff out" syndrome – acute loss of central acuity without obvious intraoperative complication
    - Decreased visual acuity - Patient only knows that they see much worse after surgery
- Glaucoma drainage implant surgery
  - Muscle imbalance – noncommitant diplopia
- Late postoperative period
  - Posterior synechiae formation – poor dilation
  - Cataract formation
  - Bleb scarring and return of high IOP
- Very late postoperative period
    - Endophthalmitis and blebitis
      - Remember "RSVP"
        - R – Redness
        - S – Sensitivity to light
        - V – Vision Change
        - P – Pain