21st Century Glaucoma Therapy

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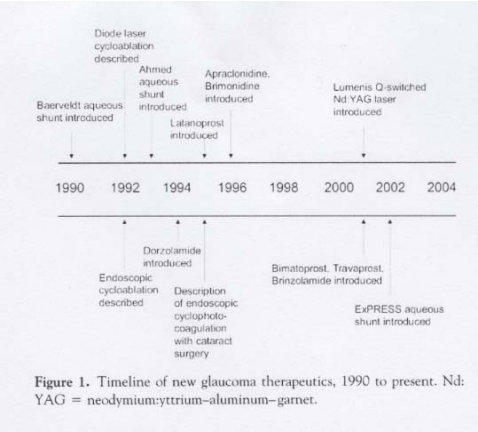

Figure 1. Timeline of new glaucoma therapeutics, 1990 to present. Nd:YAG = neodymium:yttrium–aluminum–garnet.

21st Century Glaucoma Therapy

- Recent Advances in Therapy
  - Clinical Trials
    - OHTS, EMGT, AGIS, CNTGS
  - New Medications
    - Combination agents
      - Combigan (timolol-brimonidine)
  - Revised agents
    - Travatan Z
      - Different preservative
    - Lumigan X (reduced concentration bimatoprost)- not approved in United States

21st Century Glaucoma Therapy

- Better understanding of disease pathophysiology
  - Ultrastructural - extracellular matrix, cell processes, cell-cell interaction, molecular biology
  - Risk factor assessment (IOP, age, race, heredity, corneal thickness)
- New technologies
  - Structural assessment (HRT, GDx, OCT, RTA)
  - Functional assessment (SITA, SWAP, FDT, HEP)

21st Century Glaucoma Therapy

- Evidence-based medicine
  - National Eye Institute clinical trials
  - Prospective cross-sectional and longitudinal studies
- New therapeutic approaches
  - Target IOP/Balancing efficacy, safety, and tolerability
  - Medications & Surgery
- What's else is new
  - New Medications
  - Blood Flow
  - Neuroprotection
  - Risk Assessment

The Impact of Clinical Trials on Glaucoma Management

- Questioning the role of IOP
  - Led to initiation of large, well-designed clinical trials
- Shift from practicing by tradition to that based upon evidence
- Does lowering IOP prevent or delay onset of glaucoma?
  - OHTS, EMGT, AGIS, CIGTS
- Does lowering IOP in newly diagnosed glaucoma slow progression of disease?

The Impact of Clinical Trials on Glaucoma Management

- Can Risk Factors be Identified?
  - Who is at highest risk of developing glaucoma or progressing to disabling visual loss?
- Clinical trials provide insight into many of these questions

Protocol for Glaucoma Therapy How Will This Model Change in the Future?

- 1st line PGs
  - Latanoprost becoming a generic in 2011
  - How will this shake things up?
- 2nd medication
  - Topical CAI or Beta Blocker or Alpha agonist
- 3rd Line
  - Fixed Combination agents
    - or
  - ALT/SLT
- How will this model vary in the future?

Future Glaucoma Agents Cytoskeletal Agents

- Cytochalasins
- Ethacrynic acid
- Tricrynafen
- Protein kinase C activators
- Protein kinase inhibitors
  - Rho-kinase inhibitors
    - Statins

Rho-kinase Inhibitors Outflow-Enhancing Drugs

- Glaucoma medication that reduces the IOP by reducing the resistance to aqueous outflow within the trabecular meshwork
- There is an age related increase in contractile tone in smooth muscle
- Inhibition with Rho Kinase inhibitors reduces contractile tone of smooth muscle
- Increase aqueous outflow by relaxing TM tissue
  - Effect lasts for 12 hours

Rho-kinase Inhibitors

- May also improve blood flow to the optic nerve
  - Reduce vasospasm
- May be neuroprotective
- Need a target cell specific medication
  - Non specific Rho Kinase inhibitor may be undesirable effects throughout body
  - Novartis, Inspire, Santeen, Senju all working on medication

21st Century Glaucoma Therapy

- Adenosine receptor agonists
  - Enhance extracellular matrix turnover in the trabecular meshwork
  - Outflow enhancing agent

21st Century Glaucoma Therapy

- Drug Delivery Devices
  - Started 35+ years ago with the Ocusert
  - Devices now available to implant materials in vitreous
  - Still need stable anterior segment device such as
    - Extended wear contact lens
    - Punctal plug

21st Century Glaucoma Therapy

- Contact Lens Drug Delivery Device
  - Pros
    - Consistent, sustained, efficient delivery of medication
    - Little waste
    - Enhanced compliance
    - Reduced side effects since more even drug
    - Cons
    - Cost
    - Fall out and no agent going to eye
    - Insertion technique

Punctal Plug Drug Insertion System QLT, inc.

- Currently filled with Latanoprost
- Concept is for drug core to last for 90 days
  - Improve drug adherence
- Retention is a concern requiring further modification of punctal insert
  - 75% retention rate at 30 days
- 22% IOP reduction
  - Only 14 drops released in 30 days
  - Explains moderate efficacy
  - Drug core release is being optimized to improve release

Surgical Procedures

- Where is their place in the glaucoma tx paradigm?
- Will they be safe enough to move up to primary therapy?
- Will SLT become a primary agent?
- Will the trabeculectomy be replaced by safer procedures?

Where We Are Going

- Glaucoma drainage implants
- New surgical approaches
  - Express implant
  - Trabectome
  - Glaukos trabecular bypass micro-stent
  - Eyepass glaucoma implant
  - Canaloplasty
  - Miami-Inn Focus Drainage Implant (MIDI)
  - Small-diameter aqueous shunt
  - Gold-micro shunt
  - Excimer laser trabeculostomy (ELT)

What is Neuroprotection?

- Preservation of RGCs that were damaged or undamaged at the time of initial injury, but remain at continued risk for further damage, dysfunction or death
- Neuroprotection is a direct means of preventing RGC death independent of IOP reduction

Factors Affecting RGC Injury in Glaucoma

- Primary insult (e.g. elevated IOP)
- Secondary (collateral) damage to adjacent cells
- Local environment
- Systemic factors

OCULAR PERFUSION PRESSURE AND OAG- A POSSIBLE LINK?

- As a general definition, ocular perfusion pressure is expressed as the difference between the blood pressure (BP) and the intraocular pressure (IOP)
- Therefore, depending on the blood pressure measurement used for the calculation, it is necessary to specify whether one refers to systolic, diastolic or mean perfusion pressure

Ophthalmic Perfusion Pressure

- Ophthalmic Perfusion Pressure (OPP) usually calculated as
- Mean Arterial Blood Pressure (MAP) minus Intraocular Pressure (IOP)
  - OPP=MAP-IOP
- MAP=Diastolic Blood Pressure + 2/3 (Systole-Diastole)

OCULAR PERFUSION PRESSURE AND OAG- A POSSIBLE LINK?

- Adequate perfusion is key to maintain normal tissue function
- Low ocular perfusion pressure at the optic disc may be deleterious by causing ischemia and decreased blood flow, thus leading to glaucoma damage
- Vascular dysregulation has been proposed as an important mechanism in this process
  - may cause unstable perfusion pressure with wide fluctuations, e.g., with nocturnal dips.

Risk Assessment

- Concept comes from Framingham Heart Study
  - Begun in 1948 in Framingham, MA and continues to this day
  - Just after WWII, cardiovascular disease (CVD) was recognized as important contributor to morbidity and mortality in US
  - Little was known of causes for heart disease
  - Objective was to follow a group of individuals over a longer period of time to identify characteristics contributing to CVD

How Can This Strategy Be Applied to Glaucoma?

- Identify patients at moderate to high risk of converting from ocular hypertension to glaucoma
- Direct therapy at those who are at greatest risk
- Which risk factors should be considered to note which patients are at greatest risk?