A Roadmap for Identifying and Managing Progression in Glaucoma

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Disclosures

Michael Chaglasian
• Aerie, Allergan, B+L, Equinox, Carl Zeiss Meditec, Ivantis,
Heidelberg Engineering, Optos, Topcon

Risk Factors for Progression

• For patients diagnosed or at risk of glaucoma
  • Stage disease
  • Assess risk for progression
  • Develop treatment plan
  • Surveillance
    • Establish adequate baseline testing
      • IOP
      • Visual fields
      • Imaging
      • Photographs

Risk Factors for Progression

• Once the diagnosis of glaucoma is made, the challenge is to prevent further deterioration
• If change does occur, detect it quickly
• Understanding which individual is at increased risk to get worse allows the clinician to individualize management such as:
  • Monitor closer
    • See at earlier intervals and do more frequent testing
  • Be more aggressive such as having a lower target IOP
  • Be quicker to advance therapy

Risk Factors for Progression

• Detecting change is a difficult task requiring periodic testing (photos, imaging, visual fields) performed over time
• Change may occur at any time
• Change does not occur at the same rate over the patient’s lifetime
• Due to test variability, just because a test is different (worse) from the previous one does not mean the person got worse
• Need to always confirm that change has occurred

Risk Factors for Progression

• Ability to discriminate true change, over and beyond measurement variability, is a requirement for any progression technique
  • Perimetry or Imaging
  • Progression may be measured by
    • Structural changes at the optic nerve head, retinal nerve fiber layer and macula
    • Functional changes noted as deterioration in the visual field
How Often Do Patients Get Worse Quickly?

Identify those at risk.
Treat them more aggressively.

Risk factors for Progression

- Older age
- Extent of damage at time of diagnosis
- Based upon fields, optic nerve & RNFL appearance and OCT results
- Higher IOP (peak)
- Bilateral loss – damage in both eyes
- Disc hemorrhage - is this a risk factor or a sign of damage?
- Central visual field loss – within central 10°
- Cornea hysteresis – reduced < 9.5
- Family history of progression
- Pseudoexfoliation glaucoma
- Higher Myopia - > -6.0

Risk factors for progression - EMGT

- Treatment and follow-up IOP
- Age
- Bilateral loss
- PXE glaucoma
- Disc hemorrhages
- Thinner central corneal thickness
- Lower systolic perfusion pressure
- Lower systolic blood pressure
- Cardiovascular disease

References:
- Rates of Glaucomaticus Visual Field Change in a Large Clinical Population
- How Often Do Patients Get Worse Quickly?
Predictive Factors for Glaucomatous Visual Field Progression - AGIS

- Increasing age and greater IOP fluctuation increase odds of VF progression by 30%
  - For each 5-year increase or 1 mm Hg increase
Risk factors progression – non glaucoma

• Higher myopia
• Older age

Risk factors

• Diabetes associated with RNFL thinning over time
• Over 3 years, RNFL change in part related to aging and in part related to having diabetes
  • Controls 96.2 > 95.0 um
  • ~0.4 um/year
  • Diabetics w/o retinopathy 93.5 > 90.3 um
  • ~0.3 um/year
  • Diabetics with NPDR 90.4 > 86.6 um
  • ~1.1 um/year

How Quick Will Progression Appear in a Glaucoma Patient?
A Road Map for Glaucoma Progression

Summary

Background: Treatments for open-angle glaucoma aim to prevent vision loss through lowering of intraocular pressure, but in our experience, no placebo-controlled trials have assured visual function preservation, and the observation periods of previous placebo-controlled trials have typically been at least 1 year. We assessed vision preservation in patients given timolol mesylate compared with those given placebo.

Methods: In this randomized, triple-masked, placebo-controlled trial, we enrolled patients with newly diagnosed open-angle glaucoma at 3 UK centers (patients select centers, teaching hospitals, and district general hospitals). Eligible patients were randomly allocated (1:1) with a web-generated randomization schedule, blinded in center and with a stratified block design, to receive timolol mesylate 0.5% (timolol group) or placebo (placebo group) once daily. The primary outcome was a decrease of at least 30% in visual field score (VF score) in at least one location, measured at 18 months. Analyses were adjusted for withdrawals without censoring. The data and safety monitoring committee (DSMC) recommended stopping the trial in 6 months after 30 patients had been recruited, and suggested a change in primary outcome from the difference in proportion of patients with visual field progression between groups to the loss of visual field deterioration within 12 months. The trial was registered, number NCT02618026.

Findings: We enrolled 66 patients between Dec 1, 2008, and March 10, 2010. Baseline mean intraocular pressure was 18.4 mm Hg (SD 4.6) in 21% patients in the timolol group and 18.7 mm Hg (SD 4.7) in 21% patients. At 12 months, mean intraocular pressure was 15.9 mm Hg (SD 5.3) in 121 patients assigned to the timolol group and 15.9 mm Hg (SD 5.5) in 120 patients assigned to the placebo group. Visual field progression was significantly longer in the timolol group than in the placebo group (34% vs 69% at 30 months). No significant differences in side effects were noted between the study groups. The study was stopped prematurely after 30 patients were enrolled.

Interpretation: This is the first randomized placebo-controlled trial to show preservation of the visual field with an open-angle glaucoma-treating drug in patients with open-angle glaucoma. The study design enabled significant differences in vision to be assessed in a relatively short observation period.

Procedures

We did visual field testing, intraocular pressure measurement, and imaging at 11 scheduled visits over 18 months, with clustering of the visits at baseline, 18 months, and 24 months. In each visit, visual field testing was performed over 24 months. We measured visual function through testing of the visual field. The visual field was

UKGTS

- You can see progression in as little as one year, but it requires extensive visual field testing
- Not doable in today’s practice environment
- Still can modify this since some people will progression quickly and need intervention

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What are the recommendations for determining progression and rate of progression?

- Perform sufficient examinations to detect change (usually 6 or more)
  - European Glaucoma Society
- Six visual field examinations should be performed in the first 2 years
- Measure the rate of visual field progression
- Use the same threshold test
- Pay attention to examination quality

How many fields per year? And When?

- At 1 field/year, > 10 years to detect progression
- At 3 fields/year, find average loss in 4 years, catastrophic in 2 years

Tip = Do 5-6 tests in first 2 years!

- 3 fields in first year
  - At Diagnosis, 6 months, 12 months
- Then every 6 months for next 12 months
- Allows good identification of fast, severe progressor
- Scale back to 1/year if stable

Glaucoma Progression

- The Future
  - Software that integrates imaging and visual field results
  - Neural network approach using artificial intelligence
  - Currently machines only provide spatial correlation between visual fields and imaging
  - OCT Angiography
Glaucoma Progression

- Glaucoma progresses slowly with high variability
  - Change is often non-linear
- Perimetry and OCT are complimentary methods to detect change
- Stereo photography and 2-D photography may detect early change but difficult and tedious to use
  - Difficult to see cup/disc ratio change unless large change has occurred
- Imaging provides quantitative measurements that improves ability to detect progression

What is the pattern of optic nerve change?

- Tools
  - Structural - Optic Disc and RNFL and Macula
    - Photographs
    - Imaging - OCT
    - RNFL and C/D ratio
    - RNFL and Macula GCC Guided Progression Analysis (GPA)
    - OCTA – The Future
  - Functional
    - Perimetry
      - Glaucoma Progression Analysis (GPA)
    - Overview protocols
    - Electro-diagnostic testing (PERG)

Glaucoma Progression

- The best method to detect progression varies depending upon the stage of disease
  - Early (Mild) – Structure
    - Floor effect at approximately 55um
  - Moderate to Advanced- Function
The Glaucoma Continuum

**Glaucoma Progression**

- Historically progression determined by
  - Evaluating optic nerve in real time and comparing with old photographs
  - Decide if most recent picture indicates change
  - OR
  - Evaluating visual field printouts, either single field or overview, by inspection to see if more points flagged on most recent field

It is difficult to detect progression with fundus photographs

There is often not agreement among clinicians about who is getting worse

Field Variability is also a problem

Is One Test Better than Another to Detect Change?

Structure vs. Function
Using the Proper *Tools* for Monitoring Glaucoma with Progression Analysis

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Monitoring for Progression

- **Essential Elements:**
  1. Series of good quality Visual Field tests
  2. Series of good quality RNFL and GCA tests
  3. Variety of Progression/Serial Reports

Variety of Progression Reports:

Patient Example
Summary Conclusions: Must Use Both

**Disease Stage Matters:**
- More severe disease at baseline: **VF has edge**
- Early disease at baseline: **OCT has edge**

- Also noted, patients with:
  - More follow up visits ($\geq 12$): **VF performed better**
  - Fewer follow up visits ($\leq 8$): **OCT was better**

### 3 Tools to Identify Progression:

- **Event Analysis**
  - Comparison to baseline
  - Is there statistically significant change?

- **Trend Analysis**
  - Quantifies change over time
  - Rate of change
  - Predict future change

- **Mental analysis**
  - (most important)

### Measured Progression: Trend Analysis

- **Trend Analysis**
  - "Measures the rate of change"
  - A regression line is drawn to determine rate of change for all the data that has been collected over time.
  - Using **VFI** (Visual Field Index) or **RNFL thickness**
  - A percentage rate of change (slope) is calculated
  - Most valuable when multiple VF tests have been completed
  - **Good for identifying fast progressors and generalized, large defects**
Looking at the Trend using VFI
Trend is plotted in % / year

The graph gives a prediction of future progression, if the current trend is maintained

Possible Progression= ≥1.0% VFI/yr

Likely Progression= ≥1.5% VFI/yr

Stable with Local Defect

Rapidly Progressing
Significant rate of Progression?

Key Points:

- **Visual Field Rates of Progression**:
  - Slow = < 0.5 dB/yr
  - Fast = 0.5 - 1.0 dB/yr
  - Very Fast = > 1.0 - 1.5 dB per year or higher

However, slower rates in younger patients are still at risk due to longer life with disease.


Note: This is in dB, not VFI. dB ≠ VFI.

Rapid Progression Example

- MD values:
  - 1 dB
  - 5 years: \(-5 \text{ dB} \text{ per yr} \) (off the chart fast!)

Example: Glaucoma diagnosed at 50 yrs

- Average 50 yo pt. Progressing @ -0.6 dB/year
  - 20 years to -12dB
  - defined as severe VF
  - 17 more yrs to -22dB
  - defined as "legal blindness"

Take Home:

- Identify Rate of Change ASAP

CASE WS

- 65 yo Patient
- POAG:
  - OD worse than OS
  - Pre Tx IOP: 32 OD; 24 OS
- Currently: 19 OD; 17 OS
  - On PGA, FC, s/p SLT OD
  - ONHs and VFs =>

Right Eye 7 Year Difference
Roadmap for Glaucoma Progression

Review: Range of Grayscale MD

- MD = -4 db
- MD = -12 db
- MD = -29 db

Staging Severity
- Early = < -6 db
- Moderate = < -12 db
- Severe = > 12 db

(Stages based on Hoddap-Parrish-Anderson criteria)

AGS and ICD10 Staging of Severity

- Mild Glaucoma
- Moderate
- Severe

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Measures of Progression: Event Analysis

- Event Analysis
  - Asks "Has this changed", compared to baseline an appearance on consecutive tests
  - Point by Point basis
  - Mostly used in early follow up time period
  - But also helpful in middle and late stages
  - Good for slow progressors and focal defects
  - Look for shaded triangles indicating a single point that is worsening over consecutive tests

Event Progression Analysis

Point by Point Progression Analysis
- Shows which point have progressed from baseline
**GPA Summary Report:**

- Trend Line looks +/- okay, Event Analysis is NOT!

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**Slow Progression May Still Be Vision Threatening:**

Central VF defects can affect visual function.

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**How is possible to have patients perform all of this visual field testing?**

**Faster Testing Strategies**

- SITA Faster testing takes about two-thirds of the time required by SITA Fast and about half the time required by SITA Standard.
- Test time reductions are largest in eyes with severe field loss.
- And by about one-third compared to SITA Fast.
- Many patients are able to complete SITA Faster 24-2 testing in about 2 minutes.
- (SITA Faster is only available for 24-2).
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**SITA Faster: Comparison and Validation**

- Typical test time ranges in minutes (mean +/- std. dev.)

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**SITA Standard: 4:32**

**SITA Faster:**
Detecting **Structural** Progression of Glaucoma

What tools do we have currently?
How are they used?
What is the evidence to support the use?
How can changes resulting from aging be differentiated from true progression?
Better than Visual Fields?

**Event Based**

**OCT Progression Report**

**Trend Based**

**RNFL “Event” Analysis**

- Two baseline exams are required
- Yellow Coded: Change greater than test-retest variability.
- Red: Confirmed on follow up.

**OCT “Trend” Analysis**

Four Parameters: Average, Superior, Inferior RNFL; Average C/D Ratio

**TSNIT Analysis**

- TSNIT values from baseline and current exams are plotted.
- Areas of statistically significant change are color-coded yellow when first noted and then red when the change is sustained over consecutive visits.
Legend summarizes GPA analyses and indicates with a check mark if there is possible or likely loss of RNFL:
- RNFL Thickness Map Progression (best for focal change)
- RNFL Thickness Profiles Progression (best for broader focal change)
- Average RNFL Thickness Progression (best for diffuse change)

**Case Example:** Progression Left Eye?

**CASE AA**
66 yo, AAM
HTN, Cholesterol, Anxiety Disorder,
IOP = 27, 26 mmHg OD and OS
CCT = 550
CASE BB
12 year history of OAG
Left eye with visual field defect

POAG, Normal IOPs (NTG)
- 47 yrs old
- GAT = ~21-23 mmHg OD and OS
- Asymmetric Cupping
- CCT= 520 OD/OS

GPA at Two and Three Years Follow Up.
- 3.8%
- 3.2%