Glaucoma: Clinical Trials Summary

Shawn Cohen

MDCM, FRCSC, DABO
Assistant Professor of Ophthalmology
McGill University
Let your treatment have a goal!

What RANGE of IOP should one aim for in a particular patient’s eye?
Outline

- Review of Major Trials / Studies
  - Role of IOP in Glaucoma
- Target IOP: Definition and Approach
- Canadian Consensus
- Summary
IOP - relevance to glaucoma

- The higher the IOP the greater the risk of optic nerve damage
- Corollary: lower IOP is beneficial to health of nerve. Based on AGIS data, 95% of progression in POAG is pressure-dependent and avoidable (Palmberg)
Gold standard evidence to support the concept of IOP lowering

**Recent prospective randomized clinical trials:**
- Collaborative Normal Tension Glaucoma Study Group
- The Advanced Glaucoma Intervention Study
- The Collaborative Initial Glaucoma Treatment Study
- Ocular Hypertension Treatment Trial
Normal Tension Glaucoma Study (NTGS) AJO 1998;126:498-505

Purpose:
- To determine if IOP plays a part in the pathogenesis of NTG by determining if the rate of progression is changed in eyes in which the IOP is substantially lowered

Main outcomes:
- Progression of visual field
- Change in Optic nerve

Secondary outcome:
- Decrease in visual acuity
Normal Tension Glaucoma Study (NTGS)

- Total of 230 patients enrolled
- Randomization of one eye to either:
  - No treatment (Control)
  - 30% reduction from baseline IOP by medical or surgical means
  - Target IOP of 30% lowering chosen arbitrarily (believing that to achieve this reduction filtering surgery would be required, especially given the medical restrictions)
  - In patients undergoing a trabeculectomy, a 20% reduction accepted without going to a second surgery
Normal Tension Glaucoma Study (NTGS): Results

- 140/230 eyes randomized: 61 treated, 79 controls
- Progression to endpoint i.e. disc change or visual field loss significantly higher in the control vs. treated group (35% vs 12%)
- Time to progression longer in treated vs. control group
- When adjusted for cataract, progression of visual field was greater in the control vs. treated group
- More cataracts in treated vs. control group (38% vs. 14%)
- 65% of untreated eyes showed no further progression over 5 or more years
- Some patients continued to progress despite a 30% IOP lowering
- Subgroup analysis pending (eg. No IOP influence in males!)
Normal Tension Glaucoma Study (NTGS): Conclusions

- IOP plays a significant role in the pathogenesis of normal tension glaucoma... (subanalysis pending)
- Supports aggressive lowering IOP in patients felt to be at risk for progression
- Favorable effect of IOP reduction is shown only when the impact of cataract is removed
- As not all patients progress, treatment ideally should be low in side effects
Advanced Glaucoma Intervention Study (AGIS) AJO 2000;130:429-440

Purpose:
- To study the long-term clinical course and prognosis of surgical treatments in advanced glaucoma
- To compare two surgical treatment strategies:
  - 1) ALT -> trabeculectomy -> 2nd trabeculectomy (ATT)
  - 2) Trabeculectomy -> ALT -> 2nd trabeculectomy (TAT)

Primary outcomes:
- Decrease in visual field
- Decrease in visual acuity

Secondary outcomes:
- IOP
- Complications of surgery
- Time to treatment failure
- Extent of additional medical therapy
Predictive analysis

- 738 eyes divided into three groups based on average early (18 months) IOP measurements:
  - a) Greater than 17.5 mm Hg
  - b) Between 14-17.5 mm Hg
  - c) Less than 14 mm Hg

- There is statistically significant worsening in visual field in the >17.5 mm Hg group compared to the <14 mm Hg group

- In adjusted models, a progressive worsening of VF is associated with increasing IOP within this range

- This worsening is more marked with increasing time from randomization, during the 6 year follow-up
Advanced Glaucoma Intervention Study (AGIS): Results

Associative analysis
- 586 eyes divided into 4 groups based on the percentage of visits with an IOP < 18 mm Hg over 6 years of follow-up
  - A) 100%
  - B) 75 to < 100%
  - C) 50 to < 75%
  - D) < 50%
- There is less visual field loss in patients with IOP consistently below 18 mm Hg especially with longer follow-up
- In eyes with all measures less than 18 mm Hg, who also represent the lowest IOP’s, there is almost no visual field loss on average. There are however some patients in this group that do show progression
Advanced Glaucoma Intervention Study (AGIS): Conclusions

- Lower IOP is associated with reduced progression of visual field
- Trabeculectomy increases the risk of cataract
Purpose:
- To assess the effect on patients of two treatment approaches – initial therapy with topical medications vs. trabeculectomy in newly diagnosed open angle glaucoma patients

Primary outcomes:
- 1) Visual field progression
- 2) Quality of life

Secondary outcomes:
- 1) IOP change
- 2) Visual acuity change
- 3) Cataract development
The Collaborative Initial Glaucoma Treatment Study (CIGTS): Results

All +/- followed for 4 years, most have 5 years

**Visual field**
- Minimal VF change over ~5 year follow-up
- No significant difference between visual field scores in two groups at 5 years
- Slightly worse visual fields at early time points i.e. one and two years in the surgical group which was less significant if cataract effect was corrected for
- Other significant impacts on VF were older patients, nonwhites, diabetics and those with initially higher (worse) visual field scores
The Collaborative Initial Glaucoma Treatment Study (CIGTS): Results

Quality of life

- Few significant differences in quality of life issues between surgical and medical group including analysis of potential side effect symptoms, visual function symptoms and psychological issues relating to the disease or its treatment.

- Surgical group showed more local ocular irritative symptoms such as burning, pain, tearing and redness.
Visual acuity

- Decreased early by surgery (half a line). However, by four years the average VA in both medical and surgical groups was the same.

- More visual loss was seen in the nonwhites, older patients, diabetics.

- Increased need for cataract surgery in surgery group.
The Collaborative Initial Glaucoma Treatment Study (CIGTS): Conclusion

- Aggressive initial medical IOP management, is as effective as early surgical therapy over the follow-up reported

- No dramatic quality of life issues between groups
Ocular Hypertension Treatment Study (OHTS)

Purpose:
- To determine whether decreasing IOP by 20% and < 25 mm Hg prevents the development of POAG in patients with ocular hypertension

Outcome
- Development of specified optic nerve or visual field deterioration

Methods
- 1636 patients with ocular hypertension OU
- Randomized to treatment with ocular hypotensive medications or controls with no treatment
- Followed over minimum of five years
Ocular Hypertension Treatment Study (OHTS): Results

Results
- POAG developed in 9.5% of controls vs. 4.4% of treated patients
- Controls showed a 4% decrease in IOP vs 22% decrease in treated patients
- Multivariate analysis showed that higher IOP, larger initial horizontal and/or vertical CD ratio, older age, and greater Humphrey pattern standard deviation were predictive of development of POAG
- Thinner central cornea was also associated with the development of POAG (< 555 microns: 36% versus >585: 2%)
Ocular Hypertension Treatment Study (OHTS): Conclusions

- Topical hypotensive medication was effective in delaying or preventing onset of POAG in individuals with elevated IOP.
- The decision to treat ocular hypertensives involves many factors. Examples:
  - the relatively low risk of development of POAG (CCT)
  - the burden of long term therapy, including possible adverse effects, cost, inconvenience
  - the individual’s likelihood of developing POAG
  - the individuals health status and life expectancy
- Certain baseline factors may help predict who may develop POAG.
Large diurnal fluctuations in IOP are an independent risk factor for progression in patients with POAG. 166 patients with POAG and documented IOP measurements < 25 mmHg during 5 years of follow-up, performed home tonometry five times a day for five days. Patients were categorized based on IOP fluctuation during home tonometry among other variables. Patients were followed for progression of their glaucoma, mostly based on VF deterioration.
Target IOP Range - Definition

- “the upper limit of a stable range of pressures deemed unlikely to cause further optic nerve damage in a particular eye” (AAO, 1996)

- “the mean IOP obtained with treatment that prevents further glaucomatous damage” (EGS, 1998)

- “the IOP at which the rate of retinal ganglion cell loss is no greater than the age-related loss” (Brubaker, 1996)

- Unfortunately, no accurate method to determine precisely, what a safe level of IOP is for any given optic nerve status
Target IOP Range - Dynamic Concept

- Can vary between patients and between eyes of same patient (e.g., trauma, PEX, advanced damage to one eye)

- May change during course of the disease, especially if ongoing evidence of progression

- Needs to be continually re-evaluated

- Best to measure IOP at same time of day when starting a new medicine, and at different times of day when assessing diurnal variation
Approaches to Setting Initial Target IOP Range

- Percentage lowering
- Absolute IOP cut-off
- Formula based IOP cut-off
Approaches to Setting Initial Target IOP Range

Percentage lowering:

- AAO PPP recommends \( \geq 20\% \) lowering from baseline IOP.
- European Glaucoma Society (EGS) recommends \( \geq 30\% \) IOP lowering from baseline IOP.
- NTG collaborative study showed that 80\% of patients benefit when IOP is lowered 30\% from baseline at 5yrs, compared to only 40\% of controls in the untreated control group.
Approaches to Setting Initial Target IOP Range

Absolute IOP cut-off based on evidence:

- **Glaucoma suspect (based on elevated IOP):**
  - OHTT has shown that IOP of < 25 mm Hg can prevent or slow onset of POAG

- **Advanced Glaucoma Intervention Study (AGIS)**
  - eyes with an IOP consistently less than 18 mm Hg had almost no progression based on VF over 6yrs vs. eyes with IOP’s < 18 only 50% of the time (worsening of VF)

- **Very advanced glaucoma (near total cup with split fixation) - stability if IOP’s consistently less than 15 mm Hg (Odberg, Shirakashi and others - retrospective studies)**
Approaches to Setting Initial Target IOP Range

**Formula based IOP cut-off:**

- Collaborative Initial Glaucoma Treatment Study (CIGTS)
  
  \[ \text{Target IOP} = (1 - \frac{\text{baseline IOP} + \text{VF score}}{100}) \times \text{baseline IOP} \]

- Jampel 1997; 6:133-138
  
  \[ \text{Target range} = [\text{Initial IOP} \times (1 - \frac{\text{Initial IOP}}{100}) - Z + Y] \]
  
  +/- 1 mm Hg

  - Z is an optic nerve damage severity factor
  - Y is a burden of therapy factor
Staging each eye of a glaucoma patient

- **Suspect** - at least one of the following:
  - IOP above 22 mm Hg (adjusted for pachymetry if available)
  - suspicious disc or C/D asymmetry of $> 0.2$
  - suspicious 24-2 (or similar) Visual field defect (VFD)

- **Early** - early glaucomatous disc features (eg. $C/D \leq 0.65$) and/or mild VFD not within 10 degrees of fixation

- **Moderate** - moderate glaucomatous disc features (eg. $0.7 - 0.85$) and/or moderate VFD not within 10 degrees of fixation

- **Advanced** - advanced glaucomatous disc features (eg. $C/D \geq 0.9$) and/or VFD within 10 degrees of fixation. Also consider baseline 10-2 visual field (or similar)
Target IOP Range†

Based on the staging of the glaucomatous eyes the following are the suggested upper limits of initial target IOP range for each eye.

N.B. Modify as needed based on longevity, quality of life, risk factors for progression

**SUSPECT (IF DECISION IS MADE TO TREAT)‡**

< 25 mm Hg with at least 20% reduction from baseline IOP

**EARLY**

< 21 mm Hg with at least 20% reduction from baseline IOP

**MODERATE**

< 18 mm Hg with at least 30% reduction from baseline IOP

**ADVANCED**

< 15 mm Hg with at least 30% reduction from baseline IOP

† The lower limit of target IOP is episcleral venous pressure
‡ See OHTS
Experts Opinion
Not always a consensus...

Do you believe that the target IOP for early and moderate glaucoma as described in the Canadian Perspective in Glaucoma Management are...?
More Aggressive Rx Needed?

Initial: 26  26  26

Guide: < 21  < 18  < 15
S.C.: < 18  < 15  < 12
Evidence to Support IOP Lowering in Glaucoma

Recent prospective randomized clinical trials:

- Collaborative Normal Tension Glaucoma Study
  - Arbitrary 30% IOP lowering is effective
- Advanced Glaucoma Intervention Study
  - Aim for IOP less than or equal to 18 mm Hg at all visits
- Collaborative Initial Glaucoma Treatment Study
  - Surgical or medical therapy can be first line
- Ocular Hypertension Treatment Trial
  - 20% IOP reduction reduces progression from 9.4% to 4.4%
  - Pachymetry influences progression risk
- Early Manifest Glaucoma Trial
  - Treatment works!
  - Every 1 mm Hg IOP reduction lowers progression by 10%
But Lowering the Water Level (IOP) is NOT Enough!

- Over 90% of untreated patients with OHT do not progress to glaucoma
- Over 65% of untreated NTG patients remain stable
- Progression still occurs in treated NTG (12%) and OHT subjects (4.4%)
- IOP lowering in males with NTG has no significant effect on progression!
Goals of Therapy

- Keep the IOP below the target level at all times
- Stabilize the diurnal curve
- Treat secondary causes