decrease in the risk of progression. Thus, the IOP achieved after the initial reduction is a major predictor of future progression.

In cases where patients do not comply with their glaucoma medications or do not report for follow-up regularly, maintaining a low IOP by whatever means can be beneficial in preventing glaucoma progression. Options for maintaining persistently low IOP include potent once-a-day glaucoma medications (prostaglandin analogues), addition of laser trabeculoplasty, or glaucoma filtering surgery. These options can be used to lower the IOP with minimal effect on the quality of life of the patients. An additional 1 mm Hg difference in IOP lowering may not be much in the short term, but may mean preservation of vision in the long term. Glaucoma is a lifelong disease and the 17% reduction in the risk for progression for many years may be enough to prevent blindness.

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Collaborative Interventional Glaucoma Treatment Study (CIGTS) Interim Results[1]

Reviewed by Joseph Anthony J. Tumbocon, MD

STUDY SUMMARY

This is an ongoing randomized, controlled clinical trial designed to determine whether patients with newly diagnosed open-angle glaucoma are better treated initially with medication or immediately by filtration surgery (trabeculectomy with or without 5-fluorouracil).

Glaucomatous damage was defined by the presence of one of the following criteria:

- A qualifying intraocular pressure (IOP) of ≥20 mm Hg, with a Humphrey visual-field (HVF/standard achromatic perimetry) result that includes ≥3 contiguous points on the total deviation probability plot at the less than 2% level and a Glaucoma Hemifield Test result that is "outside normal limits," and optic discs compatible with glaucoma, or
- A qualifying IOP of 20 to 26 mm Hg, with a HVF result that includes ≥2 contiguous points in the same hemifield on the total deviation probability plot at the less than 2% level and glaucomatous optic-disc damage, or
- A qualifying IOP ≥ 27 mm Hg, with glaucomatous optic-disc damage (no required visual-field changes).

Six hundred seven (607) patients (mean age 57.5 years) from 14 clinical centers were enrolled from October 1993 to April 1997. Most were diagnosed to have primary open-angle glaucoma (90.6%). Pigmentary and pseudoexfoliation glaucoma accounted for 4.6% and 4.8% respectively. Adaptive randomization was performed. The patients were assigned to either initial medical therapy (n=307) or primary trabeculectomy ±5-fluorouracil (n=300). Visual-field scores[1,5] were generated on the basis of a weighted summary of the deficits on the Humphrey total probability plot. The two groups had similar baseline characteristics: visual-field score, visual acuity (VA), IOP, cup-to-disc ratios, age, study site, gender, race, diagnosis, family history of glaucoma, presence of hypertension and diabetes mellitus.

The patients in both groups were aggressively treated to lower the IOP to a predetermined individualized target based on the patient's baseline pretreatment IOP and visual-field score (Target IOP = (1 - [reference IOP + visual-field score]/100) x reference IOP). In the surgical arm, the patient underwent trabeculectomy within 14 days of randomization. If further treatment was required, argon laser trabeculoplasty was the first option, followed by a sequence of medications, repeat trabeculectomy with an antifibrotic agent, and medications. In the medical arm, patients received a sequence of medications that usually began with a topical beta-blocker, followed by an alternate single topical therapeutic agent, dual topical therapy, triple topical therapy, an alternate combination of triple topical therapy, and optional additional topical and/or oral medications. If further treatment was required, the next treatment step was argon laser trabeculoplasty, followed by trabeculectomy, medications, trabeculectomy with an antifibrotic agent, and medications. Criteria for intervention failure (failure to meet the target IOP or evidence of progressive visual-field loss or both) had to be met before further treatment steps were initiated. The patients were followed up every 6 months for a period of 5 years.

Primary outcome measures were visual-field loss[3] and quality of life.[4] Increasing visual-field scores reflected increasing visual-field loss. Quality of life was assessed using the Symptom and Health Problem Checklist and the Visual Activities Questionnaire (VAQ). Secondary outcome

measures were visual acuity, IOP, and cataract formation.[3]

There was no significant difference in visual-field loss and quality of life when the two groups were compared after a completed follow-up of 4 years and a partially completed follow-up of 5 years, although the quality of life measure was initially better in the medication group. In addition, there was no significant change in the visual-field scores in both treatment groups compared with baseline values. Patients who had higher visual-field deficits were associated with a greater likelihood of having complaints of dimming of vision, difficulty with distance vision, and difficulty with depth perception. The average VA in the two groups was similar. IOP was lower with surgery (IOP range of 14-15 mm Hg through 5 years from a baseline average of 27 mm Hg) than with medications (IOP range of 17-18 mm Hg through 5 years from a baseline average of 28 mm Hg). Initial surgical treatment had a higher rate of cataract formation requiring removal (17.3%) than initial medical treatment (6.2%). The frequency of treatment crossover was comparable in both the medical (8.5%) and surgical (8.3%) groups. By four years of follow-up, 27.9% in the medical group and 20.8% in the surgical group underwent laser trabeculoplasty (LTP). Supplemental LTP was effective in futher lowering IOP in both treatment arms.

COMMENTS

This is a well-conducted, randomized controlled clinical trial involving newly diagnosed glaucoma patients that utilized the concept of individualized target IOP rather than a fixed percentage IOP reduction. Aggressive treatment was used to reach the individualized target IOP in both treatment groups using a set protocol. Effect of glaucoma and its treatment on the quality of life was assessed.

There was no selection bias. By using adaptive randomization called minimization, it achieved an optimal balance between the two treatment groups regarding age, study site, gender, race, and diagnosis.

All available data at all time points were analyzed as randomized. The rates of follow-up were similar in both treatment groups from 6 months to 5 years, minimizing attrition bias.

Study limitations

This study has partially completed follow-up at five years; the last follow-up interval of 161 patients was not included in the analysis. The attrition rates, however, were similar in both treatment groups.

Five-year follow-up might not be long enough to show a difference between initial treatment with surgery versus medications. Other large glaucoma clinical trials (e.g. Ocular Hypertension Treatment Study, Advanced Glaucoma Intervention Study) showed a more significant difference between their respective treatment groups after 5 years of follow- up.

The patients, doctors, and examiners of the outcome measures were not masked to the treatment allocation, which may result in some performance and detection bias. This was unavoidable in most cases. However, interviewers for the quality of life measures were masked.

The Humphrey total deviation plot was used to detect glaucomatous visual-field defects, which may be confounded by the presence of media opacities (e.g. cataracts).

The disease status of the patients included in this study might be too mild to observe a difference between the two treatment groups.

Glaucoma progression was evaluated by visual-field deterioration alone. This may overlook eyes that had glaucomatous optic-nerve changes that have not manifested functionally on standard automated perimetry. This may lead to underdiagnosis of progression.

Laser trabeculoplasty was not viewed as an intervention with crossover implications.

The quality of life measures may be confounded by other ocular comorbidities.

IMPLICATIONS ON CLINICAL PRACTICE

The current data in this study are insufficient to determine whether medical or surgical therapy is more effective in controlling open angle glaucoma (OAG). However, the results suggest that aggressive therapy to lower IOP to a predetermined individualized target prevents visual-field deterioration in the intermediate follow-up period. Furthermore, the level of IOP reduction (surgical group 44%; medical group 35%) is higher than in some of the other large clinical trials (e.g. Early Manifest Glaucoma Trial, Collaborative Normal-Tension Glaucoma Study, Ocular Hypertension Treatment Study), which may explain why none of the eyes in this study had any significant visual-field progression. Thus, an individualized target IOP should be established for glaucoma patients based on the severity of their disease, baseline IOP and other factors. All treatment efforts should then be exerted to reach, maintain and, if needed, adjust the target IOP to prevent the progression of glaucoma.

The advent of a potent class of glaucoma medications (prostaglandin analogues/ocular hypotensive lipids) has allowed greaer lowering of IOP compared with older drugs, enabling ophthalmologists to reach treatment goals medically in a substantial number of cases. If the IOP is still not controlled with maximum tolerated medical therapy, laser trabeculoplasty and surgery are other options to control the disease. As shown in this study, laser trabeculoplasty is an effective adjunctive modality to further lower the IOP in open-angle glaucoma patients, whether medical or surgical therapy was initially utilized.

In patients who cannot afford the cost of chronic medical therapy or in whom compliance is a problem, trabeculectomy is a viable alternative as initial treatment. However, they should be warned of the higher rate of developing cataracts, which may negate the cost-effectiveness of surgical therapy.

The quality of life of patients with glaucoma appears to be negatively affected with increasing severity of the disease. It is essential that ophthalmologists educate these patients regarding the nature of their disease and provide them optimal treatment to lessen the impact on the quality of life.

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Advanced Glaucoma Intervention Study (AGIS)[1]

Reviewed by Jesus Altuna, MD

STUDY SUMMARY

The Advanced Glaucoma Intervention Study is a multicenter, prospective, randomized study on advanced primary open-angle glaucoma patients (POAG) that have failed initial medical treatment. The study assessed the outcomes of sequences of interventions involving trabeculectomy and argon laser trabeculoplasty. Specifically, the association between control of intraocular pressure (IOP) in the two treatment sequences and visual field preservation was determined.

Patients with advanced open-angle glaucoma aged 35 to 80 years old were enrolled into the study. Eligible eyes had to be phakic, on maximum tolerated medical therapy, with best corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of at least 56 letters (Snellen equivalent approximately 20/80 or 6/24, consistently elevated intraocular pressures of 18 mm Hg or greater, glaucoma visual-field defect score ranging from 1 to 16, and optic disk rim narrowing. Visual-field defect scores derived from Humphrey 24-2 threshold fields were developed for this study and range from 0 (no defect) to 20 (end-stage glaucoma).

Eyes were randomly assigned to one of two sequences of glaucoma interventions: initial argon laser trabeculoplasty followed by trabeculectomy and trabeculectomy (ATT), and initial trabeculectomy followed by argon laser trabeculoplasty and trabeculectomy (TAT).

The outcome measure is a change from baseline in follow-up of visual-field defect score. The relationship between intraocular pressure (IOP) and progression of visual-field damage over 6 or more years of follow-up was determined.

The AGIS 7 report can be viewed as a dose-response analysis. Two analyses were used by the investigators. In the predictive analysis, the "dose" was the average IOP from the first three 6-month visits. In the associative analysis, the "dose" was the percent of visits over 6 years at which the treated eye achieved target IOP (<18 mm Hg). The response for both analyses was visual-field progression. The predictive analysis was designed to assess whether IOP during early follow-up is predictive of subsequent change from baseline in visual-field defect score. Seven hundred thirty eight eyes were categorized into three groups in accordance with the average IOP over the 6th, 12th, 18th month visits: Group A (<14 mm Hg), Group B (14-17.5 mm Hg) and Group C (>17.5 mm Hg). The associative analysis is a measure of consistency of IOP control. Five hundred eighty six eyes were further categorized into four groups based on the percent of 6-month visits over the first 6 follow-up years in which eyes presented with IOP less than 18 mm Hg: Group A (100%), Group B (>75% - <100%), Group C (50% - 75%) and Group D (0% - <50%).

In the predictive analysis, eyes with average IOP greater than 17.5mm Hg had an estimated worsening during subsequent follow-up that was 1 unit of visual-field defect score greater than eyes with average IOP less than 14 mm Hg ($p = 0.002$). This amount of worsening was greater at 7 years (1.89 units; $p < 0.001$) than at 2 years (0.64 units; $p = 0.071$). In the associative analysis, eyes with 100% of visits with IOP less than 18 mm Hg over 6 years had mean changes from baseline in visual-field defect score close to zero during follow-up, whereas eyes with less than 50% of visits with IOP less than 18 mm Hg had an estimated worsening over follow-up of 0.63 units of visual-field defect score ($p = 0.083$). This degree of worsening was greater at 7 years (1.93 units; $p < 0.001$) than at 2 years (0.25 units; $p = 0.572$).

COMMENTS

This study has a long follow-up period of up to 7 years with a large sample size of 591 patients s(789 eyes). Standardized protocol was followed in all the different centers participating in the study. Eligibility measurements were separated from baseline measurements obtained for all patients once they were randomized to the two treatment sequences.