The Glaucoma Laser Trial (GLT)

2. Results of Argon Laser Trabeculoplasty versus Topical Medicines

THE GLAUCOMA LASER TRIAL RESEARCH GROUP*

Abstract: The Glaucoma Laser Trial, a multicenter, randomized clinical trial involving 271 patients, was designed to assess the efficacy and safety of argon laser trabeculoplasty (ALT) as an alternative to treatment with topical medication for controlling intraocular pressure (IOP) in patients with newly diagnosed, previously untreated primary open-angle glaucoma (POAG). Each patient had one eye randomly assigned to ALT (the laser first [LF] eye) and the other eye assigned to timolol maleate 0.5% (the medication first [MF] eye). Medication was initiated or changed for either eye according to the same stepped regimen if the IOP was not controlled. Throughout the 2-year follow-up, LF eyes had lower mean IOPs than MF eyes (1–2 mmHg), and fewer LF eyes than MF eyes required simultaneous prescription of two or more medications to control IOP ($P < 0.001$). After 2 years of follow-up, 44% of LF eyes were controlled by ALT, 70% were controlled by ALT or ALT and timolol, and 89% were controlled within the stepped medication regimen. After 2 years, 30% of MF eyes remained controlled by timolol, and 66% were controlled within the stepped regimen. There were no major differences between the two treatment approaches with respect to changes in visual acuity or visual field over the 2 years of follow-up.
Ophthalmology 1990; 97:1403–1413

Historically, the initial treatment for primary open-angle glaucoma (POAG) has been reduction of intraocular pressure (IOP) through the use of various medications. If medications fail to reduce the IOP to levels believed safe by the ophthalmologist, then surgical intervention to lower the IOP has characteristically followed. The introduction of argon laser trabeculoplasty (ALT)[1] enabled the ophthalmologist to interpose this treatment between medication and surgery in the hope that the pressure-lowering effect of the procedure would either postpone or obviate the need for surgery.

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Originally received: August 14, 1990.
Revision accepted: September 4, 1990.

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Presented at the American Academy of Ophthalmology Annual Meeting, Atlanta, Oct/Nov 1990.

Supported by grants from the National Eye Institute (EY04626, EY04614, EY05889, EY04582, EY04634, EY04563, EY05875, EY05884, and EY04945).

None of the members of the writing committee or any of the other committees of the GLT (Steering Committee, Executive Committee, Design and Quality Assurance Committee, Treatment Effects Monitoring and Advisory Committee) has a proprietary or financial interest in the treatments under evaluation. Disclosure letters are on file at the GLT Coordinating Center.

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Table 1. Design Synopsis

Type of trial
Therapeutic
Centers
8 clinics
Coordinating center
Photography reading center
Visual field reading center
Treatment groups
MF—control: stepped topical medication
LF—test: ALT with stepped topical medication applied subsequently if needed, according to same protocol as for MF eye
Outcome measures
Prescription of >1 medication
Change in visual field
Change in optic disc
Change in IOP
Change in visual acuity
Patient recruitment
Goal: 240 (480 eyes)
Achieved: 271 (542 eyes)
Selection criteria
See Table 2
Treatment assignment
Random
Eye as randomization and treatment unit
Each patient has both MF eye and LF eye
Stratification variables
Clinic
Higher pressure eye
Bias control
Masked measurement of IOP
Masked evaluation of visual fields and disc stereophotographs
Follow-up
Goal: 2 yrs
Achieved: ≥2 yrs for 93% of patients

MF = medication first; LF = laser first; ALT = argon laser trabeculoplasty; IOP = intraocular pressure.

Table 2. Selection Criteria

Inclusion
Age, ≥35 yrs
IOP in both eyes ≥ 22 mmHg on 2 consecutive visits
IOP ratio between 0.67 and 1.50, inclusive
Glaucomatous field defect in at least 1 eye or disc abnormalities in the presence of extremely elevated IOP
Best-corrected visual acuity 20/70 or better in both eyes
Informed consent
Exclusion
History or evidence of glaucoma other than POAG
History of topical or systemic ocular antihypertensive medication usage within the last 6 mos that includes:
Use of medication for >14 days
Use of >1 medication
Evaluation of efficacy of medication
Severe paracentral or generalized field defect
Contraindication for use of any of the trial medications
Previous corneal, intraocular, or laser surgery
Scarring sufficient to preclude 10° of the angle of either eye from ALT
Evidence of diabetic retinopathy, neovascularization, or rubeosis iridis
Current use of a corticosteroid, epinephrine, or clonidine
Any condition precluding or presumed to preclude reliable visual fields, disc stereophotography, or 2 yrs of follow-up

IOP = intraocular pressure; POAG = primary open-angle glaucoma; ALT = argon laser trabeculoplasty.

With confirmation of the pressure-lowering effect of ALT in patients whose IOP was not controlled by medical therapy,[2–6] the concept of using ALT as the primary treatment for POAG emerged within the ophthalmologic community.[7–10] The Glaucoma Laser Trial (GLT) was an investigator-initiated, multicenter, randomized, controlled clinical trial, funded by the National Eye Institute (Table 1). The trial was designed to evaluate the efficacy and safety of ALT as opposed to topical medication for controlling IOP in patients with newly diagnosed POAG. The objectives of the trial included evaluation of the relative efficacy of ALT versus topical medication for reducing the need for medication (primary), and evaluation of the efficacy of ALT for preserving visual function and the safety of the procedure (secondary). Each patient was assigned ALT for one eye (the laser first [LF] eye) and timolol maleate 0.5% for the other eye (the medication first [MF] eye), as dictated by randomization. Medication was prescribed subsequently for either eye if necessary to control IOP, according to the same stepped medication regimen and according to the same criteria for assessment of IOP control. The protocol was approved by the institutional review board of each participating center.

We previously have reported on the acute posttherapy effects of ALT on IOP in the GLT.[11] The trial design and methods will be reported in a future publication. We report here on the treatment results relating to IOP control and need for medication.

METHODS

PATIENT SELECTION

Selection criteria were designed to enroll newly diagnosed POAG patients who could be followed for a minimum of 2 years; patients who had been treated for POAG previously were excluded from enrollment with minor exceptions (Table 2). All patients were required to have IOP of at least 22 mmHg in each eye on two successive occasions at least 1 day and no more than 2 months apart; on both occasions, the inter-eye IOP ratio had to be no greater than 1.50. Visual field defect or optic disc abnormality compatible with POAG had to be present in one or both eyes.

The visual field was assessed using Program 32 on the Octopus 201 or 2000 (Interzeag, Northboro, MA) automated perimeter. Each patient had to complete at least one 30-series examination program in each eye before taking the examinations used for eligibility determination. The diameter of the pupil was required to be at least 2 mm, with or without pharmacologic dilation. A patient was considered to have visual field defect in an eye if a

point-by-point comparison of the patient's performance with the corresponding age-adjusted normal performance as provided by Program 32 (exclusive of the four test locations corresponding to the blind spot and the eight test locations in the top and bottom rows) indicated that (1) in at least two contiguous test locations in the 20° field, the patient's performance was at least 5 decibels (dB) worse than normal, or (2) in at least three contiguous test locations in the 30° field, the patient's performance was at least 5 dB worse than normal. The defect had to be judged glaucomatous in nature by the GLT ophthalmologist. Patients with severe paracentral loss (defined as any of the four central test locations with level $\leq$ 4 dB) or severe overall loss (defined as $\geq$22 test locations with level $\leq$ 4 dB) in either eye were not eligible for enrollment. Any patient with a root mean square fluctuation of at least 4.5 dB for either eye on the examination used for eligibility determination was excluded from enrolling.

Evidence of optic disc abnormality was assessed via funduscopy. For inclusion, patients not having a visual field defect in either eye had to have either a cup/disc ratio of at least 0.8 in combination with an IOP of at least 31 mmHg in each eye or a cup/disc ratio disparity of at least 0.3 in combination with an IOP of at least 27 mmHg in one eye and at least 31 mmHg in the other.

Patients were required to have visual acuity of 20/70 or better in both eyes. Patients with pigmentary or exfoliative glaucoma were excluded from enrolling. Patients with any condition that might preclude the reliable administration or evaluation of medications, laser treatment, visual field examinations, or disc stereophotography during follow-up also were ineligible.

The consent process was initiated at the first clinic visit to evaluate eligibility; each patient was given the consent statement and the patient information booklet.[12] Patients were given an oral introduction to the GLT and were urged to ask questions. Signing of the consent statement occurred after confirmation of eligibility and was a requirement for randomization.

The consent statement in use at each clinic was based on a prototype consent statement approved by the institutional review board of the coordinating center for the trial. Material could be added to the prototype statement as dictated by each clinic's review board, but material could not be deleted.

RANDOMIZATION

The randomization schedule for the trial was stratified on clinic and IOP level. The IOP levels in both eyes of a patient, although correlated, may not be equal. Hence, patients were assigned to one of two strata: the stratum with right eye high (and left eye low) or the stratum with left eye high (and right eye low). Patients with equal IOP in both eyes were assigned to one of these strata at random. The stratification on IOP protected the trial from the bias of having all eyes with higher IOP assigned to the same treatment group (thus putting that treatment group at a disadvantage with respect to achievement of IOP control).

The coordinating center administered the randomization schedule. Treatment assignments were revealed only after satisfactory review of a patient's entry visit forms and just before initiation of laser treatment. Once the assignment had been revealed to the ophthalmologist and/or patient, the patient was counted as enrolled.

Table 3. Argon Laser Trabeculoplasty Treatment Protocol

2 sessions, 4 wks apart
180° of trabecular meshwork treated (clockwise direction)—6:00–12:00, first session; 12:00–6:00, second session
45–50 burns, each session
Argon blue-green laser
50-μm spot size
0.1-sec power pulse
Power (600–1200 mW) adjusted to achieve blanching at the threshold of bubble formation
Beam focused to place burns straddling pigmented and nonpigmented anterior trabecular meshwork
Dexamethasone 0.1% or other anti-inflammatory drug, 4 times daily, 6 days after each session

TREATMENT

Argon laser trabeculoplasty was administered to the laser first (LF) eye by a GLT-certified ophthalmologist in two sessions, each consisting of 45 to 50 burns placed over 180° of trabecular meshwork and separated by approximately 4 weeks (Table 3). During each session, the laser was aimed to cause burns to straddle the pigmented and nonpigmented bands of the trabecular meshwork (anterior placement). Power intensity was adjusted between 600 and 1200 mW on a shot-by-shot basis to achieve blanching at the threshold of bubble formation without dislodgement or bursting of the bubble. The patient was prescribed dexamethasone four times daily for 6 days for the LF eye after each ALT session.

Treatment for the medication first (MF) eye was started on the day of the initial ALT session. Each patient was given a prescription for timolol maleate 0.5%, the first drug in the stepped medication regimen, and was instructed to start using the drug in the MF eye that evening.

The stepped medication regimen (Table 4) involved three commonly used topical ocular antihypertensive medications. Steps subsequent to timolol (step 1) were dipivefrin (step 2), low-dose pilocarpine (step 3), high-dose pilocarpine (step 4), timolol with high-dose pilocarpine (step 5), and dipivefrin with high-dose pilocarpine (step 6). If dipivefrin with high-dose pilocarpine was not sufficient to control IOP, the ophthalmologist was released from adherence to the stepped regimen and could prescribe according to his or her discretion (step 7). However, prescription of carbonic anhydrase inhibitors was discouraged.

The protocol required that medication be initiated or changed (i.e., stepped) whenever any of the following criteria were met: (1) inadequate reduction in IOP as confirmed by two consecutive IOP measurements (1–14 days apart), each at least 22 mmHg or more than 80% of the reference IOP (i.e., initially, the IOP taken 1 hour before

Table 4. Stepped Medication Regimen

Starting Time
MF eyes: upon randomization
LF eyes: variable; no sooner than 3 mos after randomization (1 mo after second ALT session)
Medication steps
Step 1: 0.5% timolol, twice daily
Step 2: 0.1% dipivefrin, twice daily
Step 3: low-dose pilocarpine,* 4 times daily
Step 4: high-dose pilocarpine,† 4 times daily
Step 5: 0.5% timolol, twice daily; with high-dose pilocarpine,† 4 times daily
Step 6: 0.1% dipivefrin, twice daily; with high-dose pilocarpine,† 4 times daily
Step 7: release from stepped regimen; treatment at discretion of GLT ophthalmologist
Conditions requiring a step in medication
Confirmed elevated IOP
Confirmed visual field deterioration
Disc deterioration
Severe adverse signs or symptoms

MF = medication first; LF = laser first; ALT = argon laser trabeculoplasty; GLT = Glaucoma Laser Trial; IOP = intraocular pressure.
* 2% if brown iris, 1% otherwise.
† 4% if brown iris, 2% otherwise.

the first ALT session); (2) visual field deterioration as confirmed by two consecutive field evaluations, each showing deterioration relative to the reference field (i.e., initially, the field taken 3 months after the first ALT session); (3) optic disc deterioration relative to the reference time, assessed via funduscopy or evaluation of disc stereophotographs (i.e., the initial reference photographs were those taken at enrollment); or (4) adverse signs or symptoms severe enough to warrant a change in medication.

Fulfillment of these criteria was assessed by the GLT ophthalmologist. Coordinating center staff monitored adherence to the protocol by reviewing data recorded on the visit forms and by evaluating the visual fields, noting failure to prescribe steps and erroneous prescription of steps. Actions judged not to be in accordance with GLT protocol were reviewed with clinic staff. Clinic staff were instructed to have patients continue with steps that had been prescribed erroneously. Similarly, "missed" steps (i.e., steps that were not prescribed although stepping criteria were met) remained "missed." Evaluation for fulfillment of the stepping criteria started anew at the next clinic visit.

Assessment of the MF eye for adequacy of IOP reduction began at the first clinic visit (regularly scheduled or interim) subsequent to the initial ALT session. Laser first eyes were not evaluated for adequacy of IOP reduction until 3 months after the initial ALT session.

Assessment of visual field deterioration for purposes of initiating or changing medication began 6 months after the initial ALT session. The reference field for this type of assessment was the field taken 3 months after the initial ALT session (as opposed to the one taken at entry, since there could have been changes in the field as a result of the initial treatment). Visual fields were examined using Program 32 on the Octopus perimeter. The first observation of deterioration required scheduling of a confirmatory field examination, preferably within 2 weeks.

A point-by-point comparison was made of the patient's performance on each of these fields to the performance on the reference field. Numeric criteria had to be met before a field could be called deteriorated; deterioration could take the form of deepening or enlargement of an existing scotoma, or development of a new scotoma.[13] If the deterioration was confirmed (i.e., observed in the same area on both of these field examinations), medication had to be stepped. The second field in the series became the new reference field (i.e., the visual field against which subsequent deterioration was assessed). If the IOP measured on the day of the second field examination was lower than the current reference IOP, the reference IOP was changed to the lower value.

Evidence of optic disc deterioration relative to the reference time was assessed via funduscopic examination and comparison of current disc stereophotographs to the reference stereophotographs. The GLT ophthalmologist was to use his or her best medical judgment to make this assessment. If medication was stepped because of optic disc deterioration, the stereophotographs assessed as showing deterioration became the new reference stereophotographs.

Medication also could be stepped because of adverse signs or symptoms (e.g., blurring, irritation, arrhythmias, etc.). Assessment as to whether the severity of the signs or symptoms warranted a change was left to the GLT ophthalmologist's discretion.

The GLT ophthalmologist was released from adherence to the stepped regimen for an eye if the eye received cataract surgery, retinal detachment surgery, or other ocular treatment that rendered adherence to the GLT protocol meaningless or potentially harmful to the patient. Such eyes were "moved" to step 7.

The general rule for evaluation for IOP control required a waiting period of at least 17 days after prescription of a medication, followed shortly thereafter by a new evaluation. Exceptions to this rule related to evaluation of MF eyes started on timolol and evaluation of eyes started on step 7. Medication first eyes started on timolol were evaluated for IOP control starting with the first clinic visit after initiation of treatment. The timing of the initial evaluation after a change from step 6 to step 7 for either eye was left to the GLT ophthalmologist.

EXAMINATION SCHEDULE AND PROCEDURES

Patients were asked to return 1 week after each ALT session for a posttherapy assessment. Subsequent regular follow-up visits were scheduled at 3-month intervals, measured from the date of the initial ALT session. All patients, including those with both eyes at step 7, followed the same schedule for regular follow-up visits.

Best-corrected visual acuity and IOP were measured at all regularly scheduled and interim visits. Medical history information and information relating to treatment for other ocular conditions were recorded, and refractive error determined, at 3 month intervals, measured from the date of the initial ALT session. Slit-lamp and visual field examinations of each eye were completed 3 and 6 months from the date of the initial ALT session, and every 6 months thereafter. Disc stereophotographs were taken 6 and 12 months after the initial ALT session, and annually thereafter. Gonioscopy was performed 3 and 18 months after the initial ALT session, and annually thereafter, measured from the 18-month visit. All visits included review with the patient of the medication prescribed for each eye.

All IOP measurements were made using a Goldmann applanation tonometer (Haag-Streit, Westville, NJ). Patients always were scheduled to have their measurements either in the morning or in the afternoon to minimize the effect of diurnal variation in IOP measurements within patients. The measurement process involved a tonometer operator and reader. Without viewing the dial, the operator adjusted the tonometer to the point where the inner borders of the two fluorescein arcs were touching each other. When instructed by the operator, the reader recorded the IOP level without announcing it and then reset the dial to 15 mmHg. Up to eight measurements (4 per eye) were required. Two measurements were made for the right eye, followed immediately by two measurements for the left eye. If the two measurements for either eye differed by at least 4 mmHg, the measurements for both eyes were rejected and the series of four measurements was repeated. The mean of the last two measurements for an eye was used as the measurement for the eye for the visit.

Visual field examinations were administered by a GLT-certified examiner according to protocol.[13] Pharmacologic dilation of the pupil was required if necessary to achieve the requisite minimum diameter of 2 mm. Subsequent to enrollment, a root mean square fluctuation of at least 4.5 dB mandated a single repeat visual field examination for the eye in question.

Disc stereophotography could be achieved by using either an Allen separator or single-frame photographs taken on both sides of the visual axis. Kodachrome ASA 25 or 64 film could be used; magnification had to be $\times 2$ to $\times 2.5$. Three stereo pairs were taken; one pair was focused on the surface of the retina, another at the middle depth of the cup, and the third at the floor of the cup.

Subjective refraction was performed by the GLT-certified refractionist according to protocol.[13] The refractive error presented below is the spherical equivalent of refraction (i.e., $\pm$ sphere + 1/2[$\pm$ cylinder]). Visual acuity charts developed for the Early Treatment Diabetic Retinopathy Study[14-16] were used to measure visual acuity with the patient using the prescription obtained via refraction. The right eye was tested before the left.

Gonioscopy was performed by the GLT ophthalmologist to examine the angle of the eye for trabecular meshwork pigmentation characteristics and existence of peripheral anterior synechiae (PAS). The number of degrees of the angle affected by PAS was noted. Peripheral anterior synechiae were classified as extending no farther than the ciliary body, extending to the scleral spur but not including the trabecular meshwork, or extending to the trabecular meshwork and higher.

TREATMENT EFFECTS MONITORING

Analyses of accumulating data were carried out by coordinating center staff at 6-month intervals for presentation to the trial's Treatment Effects Monitoring and Advisory Committee. Glaucoma Laser Trial clinic staff were not privy to data by treatment group until June 1989, 3 months before the start of data collection closeout.

Early in the trial, the Treatment Effects Monitoring and Advisory Committee recognized that there was a statistically significant difference between the two treatment groups regarding the number of medications needed to control IOP but recommended that the trial proceed with the planned minimum 2-year follow-up. This recommendation was based on recognition of the need for data to assess the duration of the pressure-lowering effect of ALT and for data to assess the more clinically relevant outcome of change in visual function.

ANALYSIS DATA SET

Data presented in this report are based on information received at the coordinating center as of May 14, 1990, on the 271 patients enrolled at the eight active clinical centers. Four former clinical centers enrolled a total of five patients; data on these five patients are not included.

Patients were enrolled between February 1984 and April 1987. Closeout of data collection began in September 1989 and was completed in November 1989. Data relating to treatment results through 2 years of follow-up are presented in this report. Six patients died before completing 2 years of follow-up, and 13 dropped out.

All but 14 of the 271 patients included in the analysis data set met the eligibility criteria listed in Table 2. Two of the 14 patients had neither visual field defect nor optic disc abnormality. The other 12 patients had more extensive visual field defect than specified in the GLT protocol for entry. However, all 14 patients were randomized and treated accordingly.

All but 3 of the 271 patients had ALT administered as specified by the GLT protocol (Table 3). One of the three patients was administered the first 180° ALT treatment but iritis developed in both eyes 15 days thereafter. The iritis persisted, and the second ALT treatment was never administered. A second patient received only the first 180° ALT treatment because the patient dropped out of the trial before the second ALT treatment could be administered. A third patient was administered the first ALT treatment to the LF eye but was mistakenly administered a 180° ALT treatment to the MF eye during the second ALT visit. The mistake was discovered during that visit,

Table 5. General Patient Characteristics

No. of patients	271
Age (yrs) (%)	
35–44	11
45–54	17
55–64	35
65–74	29
≥75	8
(median)	(61)
(mean)	(60)
Race/ethnicity (%)	
White	45
Black	43
Hispanic	9
Asian	1
Other	2
Sex (%)	
M	44
F	56
Medical conditions on enrollment (%)	
Diabetes	15
Coronary heart disease	12
Peripheral vascular disease	10
Hypertension*	37
Anemia	7
Using α-blocker	4
Using β-blocker	6
History (%)	
Family history of glaucoma	27
Used glaucoma medication previously	7
Blood transfusion for uncontrolled bleeding	8
Location (%)	
Atlanta	17
Boston	5
Chicago	9
Columbus	8
Detroit	17
Milwaukee	13
New York City	17
Philadelphia	14

* Patients were classified as hypertensive if they were taking medication for hypertension.

Table 6. Baseline Ocular Characteristics

Characteristic	LF (%)	MF (%)	*P*
IOP (mmHg) 1 hr before start of treatment			
≤21	8	8	
22	4	3	
23–25	38	37	
26–30	27	28	
31–40	20	21	
≥41	4	3	
(median)	(25)	(26)	
(mean)	(27)	(27)	0.60
Refractive error (D)			
< −4.0	6	6	
≥ −4.0 and < −1.0	14	15	
≥ −1.0 and < +1.0	47	45	0.37
≥ +1.0 and < +4.0	32	33	
≥ +4.0	1	1	
Visual acuity			
≥20/20	54	52	
≥20/25 and ≤20/40	44	45	0.72
≥20/50 and ≤20/70	2	3	
Meshwork pigmentation			
None	7	8	
Mild	55	55	0.68
Moderate	34	34	
Heavy	3	3	
Visual field defect			
Absent	14	16	
Present	86	84	0.56
Visual field indices			
Mean dB per test location	21	21	0.55
Mean defect per test location (dB)	4	4	0.55
Median no. of abnormal test locations per field	20	18	0.92
Median no. of scotomatous areas per field	1	1	0.98
Median no. of test locations in largest scotomatous area of field	11	12	0.82
Median corrected loss variance (dB^2)	5	5	0.47
No. of eyes	271	271	

LF = laser first; MF = medication first; IOP = intraocular pressure; D = diopter; dB = decibel.

and the LF eye was then administered the second 180° ALT treatment.

STATISTICAL METHODS

Each eye of each patient was included in the treatment group to which it was originally assigned regardless of the course of treatment. The paired *t* test[17] was used to test for differences between means of continuous variables assumed to follow a normal distribution; values have been grouped for presentation. The Wilcoxon paired sample test[17] was used to test for differences in distributions of eyes with respect to variables that are not assumed to follow a normal distribution, and medians rather than means are provided for these variables. Distributions of dichotomous variables were assessed by McNemar's test.[18] Distributions of polychotomous variables were compared using the Stuart-Maxwell generalization of McNemar's test.[19]

Kaplan-Meier estimates of survival curves[20] were used to evaluate the time to prescription of two or more medications simultaneously. The sign test[17] was used to assess the difference between the paired times. Time for the MF eyes was measured from the day of the initial ALT session (the time when topical medication was first prescribed), whereas time for the LF eyes was measured starting 3 months after randomization (thus adjusting for the 3-month medication-free interval accorded LF eyes by protocol).

The proportional hazards model of Cox[21] as adapted for paired, censored, failure time data with covariates by Holt and Prentice[22] was used to estimate the difference between the two treatment groups with respect to time to prescription of two or more medications simultaneously,

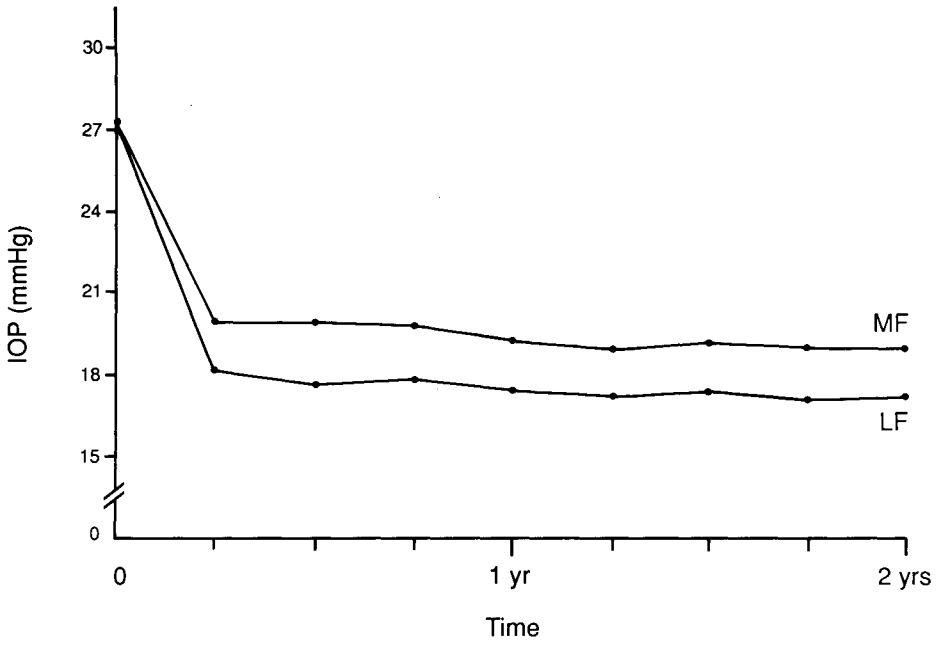

Fig 1. Mean intraocular pressure.

while adjusting for differences between the groups with respect to ocular characteristics at entry (IOP level, visual field defect, cup/disc ratio, refractive error, visual acuity, and pigmentation of the angle). To evaluate the consistency of the treatment effect, the Holt-Prentice model also was used to estimate the difference between the two treatment groups with respect to this outcome in different subgroups based on patient characteristics (age, race, sex, presence/absence of hypertension, eye color, family history of glaucoma, and clinic).

The log-rank test[23] was used to assess the difference between the time to prescription of two medications simultaneously when the times were for independent samples.

The *P* values reported herein have not been adjusted for multiple outcomes. The conventional cut-off of 0.05 was used to determine statistical significance.

BASELINE RESULTS AND COMPARABILITY OF TREATMENT GROUPS

General demographic characteristics of the study population are displayed in Table 5. The median age at entry was 61 years. The population was evenly split between whites and blacks (45 versus 43%). More females than males were enrolled (56 versus 44%).

The two treatment groups were comparable with respect to distributions of baseline ocular characteristics (Table 6). Mean IOP 1 hour before initiation of ALT was 27 mmHg for both treatment groups. The treatment groups were balanced with respect to visual acuity on entry; 98% of LF eyes versus 97% of MF eyes had visual acuity of 20/40 or better. The treatment groups also were balanced with respect to presence of visual field defect on enrollment; 86% of LF eyes versus 84% of MF eyes had field defect at entry, as defined by GLT criteria. Twenty-seven percent of patients had defect in one eye only, and 71% of patients had defect in both eyes. One percent of patients did not have visual field defect in either eye.

At entry, both treatment groups had a mean of 21 dB per test location. The median number of scotomatous areas (defined as 2 or more contiguous test locations at least 5 dB below age-adjusted normal level) per field was one for both treatment groups. The median size (i.e., the number of contiguous test locations involved) of the largest of those areas for an eye was 11 for LF eyes versus 12 for MF eyes.

TREATMENT RESULTS

Mean IOP for the LF and MF eyes is shown in Figure 1. Between entry and the 3-month follow-up visit, IOP for the LF eyes decreased by 9 mmHg, in contrast with a mean decrease of 7 mmHg in the MF eyes. Thereafter, mean IOP for LF eyes was approximately 2 mmHg below that for the MF eyes.

Table 7 displays data relating to use of topical medications to control IOP. Two years after treatment initiation, 44% of LF eyes were controlled by ALT alone, whereas 30% of MF eyes were controlled by timolol alone ($P < 0.001$). Seventy percent of LF eyes were controlled by ALT, or ALT and timolol. Eighty-nine percent of LF eyes and 66% of MF eyes were controlled within the stepped medication regimen, as of the 2-year follow-up visit ($P < 0.001$).

Table 7. Use of Medications

Prescription	3 mos LF (%)	3 mos MF (%)	1 yr LF (%)	1 yr MF (%)	2 yrs LF (%)	2 yrs MF (%)
ALT only	97	N/A	63	N/A	44	N/A
ALT or timolol	99	62	86	41	70	30
ALT, timolol, dipivefrin or pilocarpine (i.e., managed with up to a single medication)	100	97	93	68	84	51
Managed by ALT or any of the 6 medication steps	100	97	97	85	89	66
No. of patients	264		251		244	

LF = laser first; MF = medication first; ALT = argon laser trabeculoplasty; N/A = not applicable.

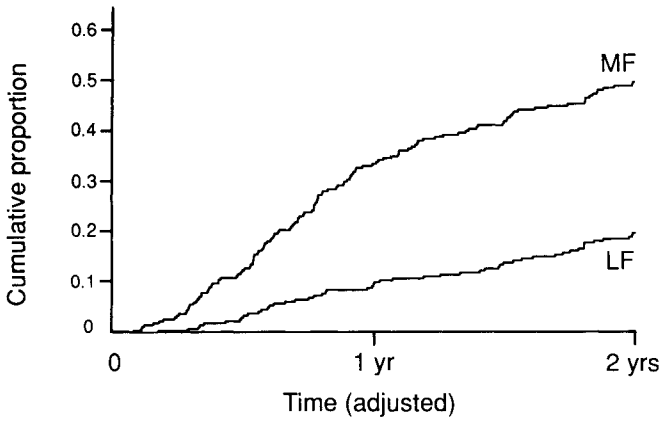

Fig 2. Cumulative proportion of eyes with simultaneous prescription of at least two medications.

Figure 2 displays the cumulative proportion of eyes in each treatment group prescribed two or more medications simultaneously (i.e., at step 5, 6, or 7 of the stepped medication regimen). At all times during the follow-up period, more MF eyes than LF eyes required two or more medications to control IOP ($P < 0.001$).

The distributions of change in visual acuity are presented in Table 8. The data indicate that visual acuity was stable in both treatment groups. The percentage of eyes improving and the percentage of eyes worsening were nearly identical in the two treatment groups, 1 and 2 years after initiation of treatment.

One of the side effects of ALT treatment is development of PAS[11,24,25]; PAS extending to the trabecular meshwork had developed in 34% of LF eyes versus 3% of MF eyes, as of the 3-month follow-up visit. The relationship of presence or absence of PAS to need for medication to control IOP is shown in Figure 3. The LF eyes with PAS to the trabecular meshwork required less medication to control IOP than the LF eyes without PAS, but the difference was not statistically significant ($P > 0.10$). Also, LF eyes with PAS had mean IOPs approximately 1 mmHg below those for LF eyes without PAS, over the course of follow-up.

Medication first eyes were prescribed approximately twice as many steps in medication as LF eyes (725 versus 365, respectively; Table 9). Reasons for stepping were similar in both treatment groups. Eighty-five percent of steps for LF eyes and for MF eyes were made because of inadequate reduction of IOP, either alone or in conjunction with another reason. Visual field deterioration, alone or in conjunction with another reason, accounted for 14% of steps for LF eyes and 8% of steps for MF eyes, although the number of steps was slightly greater for MF eyes (57) than LF eyes (50). Two percent of steps for LF eyes versus 8% of steps for MF eyes were prescribed because of adverse signs and symptoms. Signs and symptoms severe enough to warrant a change in medication are listed in Table 10, with their frequency. The most frequently cited systemic reason for a change in medication was headache. Bradycardia was cited four times as the cause for a change in medication, and tachycardia and exacerbation of asthma were each cited twice. The most frequently cited ocular symptoms associated with a change in medication were pain and blurring of vision.

Table 8. Change in Visual Acuity from Entry: Percent Distribution of Eyes by Amount of Change

Amount of Change	1 yr LF (%)	1 yr MF (%)	2 yrs LF (%)	2 yrs MF (%)
≥2 lines better	6	6	6	6
<2 line change	92	88	89	84
≥2 lines worse	3	6	5	9
P	0.96		0.94	
No. of patients	251		244	

LF = laser first; MF = medication first.

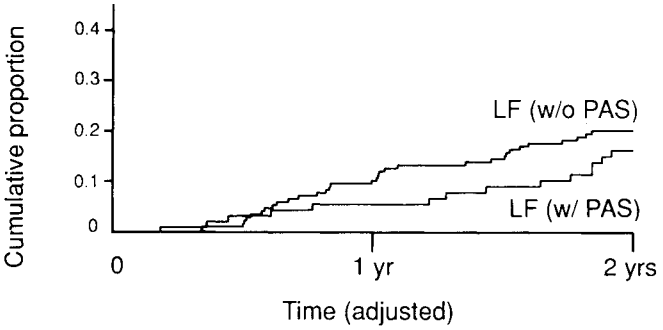

Fig 3. Cumulative proportion of eyes with simultaneous prescription of at least two medications: LF eyes with PAS to the trabecular meshwork versus LF eyes without PAS to the trabecular meshwork.

Table 9. Reasons for Implemented Steps

Reason for Step	LF (%)	MF (%)
Inadequate IOP reduction only	82	83
Visual field deterioration only	12	6
Inadequate IOP reduction and visual field deterioration	2	2
Disc deterioration	0	0
Adverse signs or symptoms only	2	7
Adverse signs or symptoms and inadequate IOP reduction	0	1
Adverse signs or symptoms and visual field deterioration	0	0
Cataract surgery	1	1
Other	0	1
Total no. of implemented steps	365	725

LF = laser first; MF = medication first; IOP = intraocular pressure.

Table 10. Frequency of Signs and Symptoms Resulting in a Change in Medication

Systemic	No.	Ocular	No.
Headache	11	Pain	24
Fatigue and weakness	7	Blurring of vision	21
Bradycardia	4	Darkening of vision	13
Mental depression	4	Hyperemia	10
Anxiety	3	Tearing	10
Dizziness	3	Periorbital edema	5
Wheezing, shortness of breath	3	Itching	2
Exacerbation of asthma	2	Photophobia	1
Tachycardia	2	Miscellaneous	10
Disorientation	1		
Hypotension	1		
Memory loss	1		
Muscle weakness	1		
Miscellaneous	9		

DISCUSSION

Evidence of the GLT suggests that, within the 2-year follow-up of the trial, ALT is both effective and safe. Mean IOP for LF eyes was consistently lower than mean IOP for MF eyes over the course of follow-up, and LF eyes generally required less medication for IOP control than MF eyes. However, some caution is in order since the length of follow-up reported herein is short given the chronic nature of POAG. In addition, we should note that neither ALT alone, nor ALT with medications as needed, nor medication alone represents a "magic bullet." Two years after the start of treatment, over half of the LF eyes (56%) required the addition of one or more medications for control of IOP. Over two thirds of the MF eyes (70%) required new or additional medication to control IOP.

Analysis by subgroups based on baseline characteristics has shown that fewer medications are needed by LF eyes than MF eyes in all identifiable subgroups based on age, race, sex, presence/absence of hypertension, eye color, family history of glaucoma, and clinic.

There was concern that the GLT design, involving eye as the randomization unit, would lead to underestimation of the amount of medication required in the LF eyes because of the so-called crossover effect of timolol (i.e., the effect of timolol in one eye lowering the IOP in the patient's other eye).[26,27] However, that effect is small in this population; the mean size of this effect was approximately 0.5 mmHg (95% confidence interval = [0.00, 1.05]), meaning that the use of timolol in the MF eye resulted in a reduction of approximately 0.5 mmHg in the IOP of the LF eye. That difference alone is not large enough to account for the observed difference between LF and MF eyes in mean IOP (2 mmHg) over the course of follow-up (Fig 1). The crossover effect of timolol observed in the GLT will be discussed in detail in a future publication.

The only side effect of ALT noted was PAS. In 34% of LF eyes versus 3% of MF eyes, PAS extending to the trabecular meshwork had developed within 3 months of initiation of treatment. The prognostic importance of the PAS remains unclear. However, at least within the follow-up period of this trial, the PAS appear to have no adverse implications regarding IOP control. If anything, IOP control is better in LF eyes with PAS than in LF eyes without PAS. Laser first eyes with PAS at 3 months had lower mean IOP than LF eyes without PAS throughout follow-up. Similarly, a smaller proportion of LF eyes with PAS than LF eyes without PAS required two or more medications to control IOP throughout the first 2 years of follow-up (Fig 3). The difference, although not statistically significant, remained even after stratification on iris color; iris color was the major predictor for PAS formation in the GLT.[11]

Compliance with the protocol was good. Overall, 98% of steps for each treatment group were prescribed in accordance with the rules for stepping. Two percent of steps prescribed for each treatment group were prescribed erroneously (i.e., because of errors in application of the protocol). Fourteen steps were missed in the MF treatment group versus seven in the LF treatment group.

Compliance in taking prescribed medications, as reported by patients at regular follow-up visits upon questioning about each eye, also was good. Patients reported that they were compliant "most of the time" (93% for LF eyes versus 92% for MF eyes, over all visits). Although we cannot be sure that medications always were applied to the eye for which they were prescribed, few mixups appear to have occurred.

One advantage of the GLT design is that the composition of the treatment groups with respect to patient characteristics was, by definition, comparable because each patient contributed one eye to each treatment group. Hence, the only characteristics that could differ by treat-

ment groups were ocular characteristics. However, the treatment groups were comparable with respect to these characteristics (Table 6). Also, the magnitude of the treatment effect was essentially unchanged after adjustment for differences in these characteristics using paired survival analysis with covariates. Thus, none of the ocular characteristics examined was found to account for the observed difference between the treatment groups with respect to need for medication.

The GLT is one of a small number of studies aimed at evaluating ALT as an initial treatment for POAG,[9,28–30] and, in general, the GLT results are consistent with the results of these other studies. Tuulonen et al[29] reported that 53% of eyes treated initially with ALT were successfully controlled by ALT alone 1 year after ALT initiation, whereas Searle et al[30] reported a success percentage of 39% (different criteria). The incidence of PAS seen in the LF eyes of the GLT is higher than the incidence in previously reported series,[24,25] but that may be due in part to the method of grading PAS.

As in any clinical trial, the population studied in the GLT represents a selected group of patients. To be enrolled, patients had to meet specific IOP requirements and had to be newly diagnosed. The eligibility criteria relating to visual field defect were designed to permit enrollment of patients with minimal defect and to exclude patients with little visual field remaining. The enrolled patients exhibited a range of visual field defect on entry (Table 6). Subsequent to enrollment, ALT treatment was administered according to an explicit protocol, and medication was prescribed according to a stepped regimen not usually followed in routine practice. Hence, inference of the findings of this trial to a more general population of POAG patients (e.g., including previously treated patients) and more general methods of treatment, must be made on a judgmental, rather than statistical, basis.

The ultimate test for any treatment for POAG is its efficacy to preserve visual function. Not surprisingly, within the first 2 years of follow-up in the GLT, differences between the treatment groups with respect to changes in the visual field were minimal; for both LF and MF eyes, a mean change of less than 1 dB per test location was found. Follow-up of the GLT patients is continuing, and the differences between the treatment groups will be assessed and discussed in subsequent articles.

Limitations and caveats notwithstanding, the results of the GLT are encouraging regarding the usefulness of ALT as an initial treatment for POAG. It appears that ALT is at least as good as if not better than starting with medications, because in the short term, ALT provides good pressure control and has the advantage of postponing and/or reducing the inconvenience, nuisance, and side effects associated with taking medications.

PARTICIPATING PERSONNEL

A list of participants in the GLT Research Group as of January 1989 appears at the end of The Glaucoma Laser Trial. I. Acute effects of argon laser trabeculoplasty on intraocular pressure. *Arch Ophthalmol 1989; 107:1135–42.*

Clinical centers:

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Steering Committee: Hugh Beckman, MD (*Chairman*); Milana Isaacson; Joseph Krug, Jr., MD; Natalie Kurinij, PhD; Curtis Meinert, PhD; Ronald Radius, MD; Robert Ritch, MD; George Spaeth, MD; Alice Sternberg, ScM; M. Angela Vela-Thomas, MD; Paul Weber, MD; Jacob Wilensky, MD. **Executive Committee:** Curtis Meinert, PhD (*Chairman*); Hugh Beckman, MD; Milana Isaacson; Natalie Kurinij, PhD; Alice Sternberg, ScM. **Treatment Effects Monitoring and Advisory Committee:** John Lachin, ScD (*Chairman*); David Dueker, MD; Douglas Gaasterland, MD; Paul Kaufman, MD; M. Cristina Leske, MD, MPH. *Non-voting:* Hugh Beckman, MD; Natalie Kurinij, PhD; Maureen Maguire, PhD; Curtis Meinert, PhD; Alice Sternberg, ScM. **Design and Quality Assurance Committee:** Hugh Beckman, MD; Milana Isaacson; Natalie Kurinij, PhD; Maureen Maguire, PhD; Curtis Meinert, PhD; George Spaeth, MD; Alice Sternberg, ScM; Jacob Wilensky, MD.

REFERENCES

1. Wise JB, Witter SL. Argon laser therapy for open-angle glaucoma: a pilot study. Arch Ophthalmol 1979; 97:319–22.
2. Schwartz AL, Whitten ME, Bleiman B, Martin D. Argon laser trabecular surgery in uncontrolled phakic open angle glaucoma. Ophthalmology 1981; 88:203–12.

3. Wilensky JT, Jampol LM. Laser therapy for open angle glaucoma. Ophthalmology 1981; 88:213–7.
4. Wise JB. Long-term control of adult open angle glaucoma by argon laser treatment. Ophthalmology 1981; 88:197–202.
5. Thomas JV, Simmons RJ, Belcher CD III. Argon laser trabeculoplasty in the presurgical glaucoma patient. Ophthalmology 1982; 89:187–97.
6. Wilensky JT, Weinreb RN. Low-dose trabeculoplasty. Am J Ophthalmol 1983; 95:423–6.
7. Migdal C, Hitchings R. Primary therapy for chronic simple glaucoma: the role of argon laser trabeculoplasty. Trans Ophthalmol Soc UK 1984; 104:62–6.
8. Rosenthal AR, Chaudhuri PR, Chiapella AP. Laser trabeculoplasty primary therapy in open-angle glaucoma: a preliminary report. Arch Ophthalmol 1984; 102:699–701.
9. Thomas JV, El-Mofty A, Hamdy EE, Simmons RJ. Argon laser trabeculoplasty as initial therapy for glaucoma. Arch Ophthalmol 1984; 102:702–3.
10. Tuulonen A. Laser trabeculoplasty as primary therapy in chronic open angle glaucoma. Acta Ophthalmol 1984; 62:150–5.
11. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial: I. Acute effects of argon laser trabeculoplasty on intraocular pressure. Arch Ophthalmol 1989; 107:1135–42.
12. Glaucoma Laser Trial Research Group. A Guide for Patients. Available from: National Technical Information Service. 5285 Port Royal Road, Springfield, VA 22161. (Accession # PB86–109741.)
13. Glaucoma Laser Trial Research Group. Handbook. Available from: National Technical Information Service. 5285 Port Royal Road, Springfield, VA 22161. (Accession # PB86–101037.)
14. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am J Optom Physiol Optics 1976; 53:740–5.
15. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982; 94:91–6.
16. Ferris FL III, Sperduto RD. Standardized illumination for visual acuity testing in clinical research. Am J Ophthalmol 1982; 94:97–8.
17. Zar JH. Biostatistical Analysis. Englewood Cliffs, NJ: Prentice Hall, 1974; 121–9, 290–1.
18. Fleiss JL. Statistical Methods for Rates and Proportions, 2nd ed. New York: John Wiley and Sons, 1981; 113–9.
19. Fleiss JL, Everitt BS. Comparing marginal totals of square contingency table. Br J Math Stat Psychol 1971; 24:117–23.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–81.
21. Cox DR. Regression models and life-tables. J Roy Stat Soc [Ser B] 1972; 34:187–220.
22. Holt JD, Prentice RL. Survival analyses in twin studies and matched pair experiments. Biometrika 1974; 61:117–30.
23. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York: John Wiley and Sons, 1980; 16–9.
24. Traverso CE, Greenidge KC, Spaeth GL. Formation of peripheral anterior synechiae following argon laser trabeculoplasty. A prospective study to determine relationship to position of laser burns. Arch Ophthalmol 1984; 102:861–3.
25. Rouhiainen HJ, Terasvirta ME, Tuovinen EJ. Peripheral anterior synechiae formation after trabeculoplasty. Arch Ophthalmol 1988; 106: 189–91.
26. Zimmerman TJ, Kaufman HE. Timolol: dose response and duration of action. Arch Ophthalmol 1977; 95:605–7.
27. Zimmerman TJ, Kass MA, Yablonski ME, Becker B. Timolol maleate: efficacy and safety. Arch Ophthalmol 1979; 97:656–8.
28. Migdal C, Hitchings R. Control of chronic simple glaucoma with primary medical, surgical and laser treatment. Trans Ophthalmol Soc UK 1986; 105:653–6.
29. Tuulonen A, Koponen J, Alanko HI, Airaksinen PJ. Laser trabeculoplasty versus medication treatment as primary therapy for glaucoma. Acta Ophthalmol 1989; 67:275–80.
30. Searle AET, Rosenthal AR, Chaudhuri PR. Argon laser trabeculoplasty as primary therapy in open-angle glaucoma: a long-term follow-up. Glaucoma 1990; 12:70–5.