The Low-Pressure Glaucoma Treatment Study (LoGTS)

Study Design and Baseline Characteristics of Enrolled Patients

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Objective: The Low-Pressure Glaucoma Treatment Study (LoGTS) seeks to evaluate visual field stability in low-pressure glaucoma patients randomized to intraocular pressure reduction in both eyes with topical twice daily brimonidine tartrate 0.2% versus twice daily timolol maleate 0.5%. This article describes the LoGTS design and presents baseline characteristics of the subjects.

Design: Randomized, multicenter, double-masked clinical trial.

Participants: Low-pressure glaucoma patients 30 years of age or older were identified. Exclusion criteria included an untreated pressure of more than 21 mmHg, advanced visual field loss, and contraindications to study medications.

Interventions: Randomization of both eyes to double-masked monotherapy with brimonidine or timolol. Follow-up visits included Humphrey 24-2 full-threshold perimetry, tonometry every 4 months, and annual optic disc photography.

Main Outcome Measure: Progression of visual field loss.

Results: One hundred ninety patients were randomized between 1998 and 2000. Mean age (±standard deviation) was 64.9±10.7 years. Women comprised 59.5% of the patients. Fifty-three patients (27.9%) had unilateral field loss. The 137 patients with bilateral field loss were older than those with unilateral field loss: 65.7 versus 62.3 years of age ($P<0.05$). Mean untreated diurnal intraocular pressures were similar between the eyes of the bilateral patients (mean, 15.5 mmHg in both eyes) and unilateral patients (mean, 16.0 mmHg in field loss vs. 15.6 mmHg in fellow eyes). Visual field mean deviation for all eyes was −5.4±4.7 decibels. Central corneal thickness in 168 phakic patients was 543 ± 35 μm (range, 435–655 μm); thickness was less than 500 μm in 15 eyes and was more than 600 μm in 11 eyes. Mean vertical cup-to-disc ratio for all eyes was 0.67±0.15. Unilateral field loss patients had a larger cup-to-disc ratio in the field loss eye (0.75±0.12) than the fellow eye with a normal field (0.60±0.17, $P<0.0001$). Disc hemorrhage was present at baseline in 29 patients (32 eyes).

Conclusions: The LoGTS was successfully able to recruit and enroll patients with open-angle glaucoma and statistically normal intraocular pressure into a longitudinal, prospective clinical trial comparing 2 different glaucoma medications. Baseline characteristics of note were a preponderance of females, unilateral field loss in 27.9% of participants, and frequent optic disc hemorrhage. Central corneal thickness had a normal distribution and did not account for false low-pressure measurements in LoGTS patients. *Ophthalmology 2005;112:376–385*

The term *glaucoma* describes a specific pattern of progressive retinal nerve fiber layer, optic nerve head, and visual field damage caused by a number of different diseases of the eye, all of which have an intraocular pressure (IOP)-dependent mechanism of the disease process. Low-pressure glaucoma (LPG) has been defined as chronic open-angle glaucoma (OAG) with progressive visual field and optic nerve damage, despite an untreated IOP that always measures

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within the statistically normal range (mean±standard deviation, 15.5±2.6 mmHg).[1]

Low-pressure glaucoma is reported to comprise a significant percentage of eyes with OAG.[1,2] In the Baltimore Eye Study (5308 subjects), 24% of OAG patients had an IOP of less than 21 mmHg; the prevalence of OAG was 0.65% for individuals with a screening IOP of less than 16 mmHg.[3] The Beaver Dam Eye Study (4926 subjects) reported an overall 2.1% prevalence of OAG; 32% of cases had an IOP of less than 22 mmHg.[4] In the Early Manifest Glaucoma Trial, baseline IOP was less than 21 mmHg in 69 of 129 patients (53.5%) in the treatment group and in 63 of 126 patients (50%) in the untreated control group.[5]

Evidence suggests a role for IOP as a risk factor for glaucomatous damage in LPG. Retrospective studies in LPG patients with asymmetric IOP readings report a tendency for greater visual field loss in the eye with higher pressure.[6–8] Optic nerve morphometric studies show a decline in neuroretinal rim area with increasing IOP in LPG patients.[9,10] Results of the prospective, randomized Collaborative Normal-Tension Glaucoma Study demonstrate that a 30% therapeutic reduction of IOP slows the rate of glaucomatous optic nerve or visual field progression.[11,12]

Clinical studies suggest that conventional treatment to lower IOP is beneficial in glaucoma management; however, IOP reduction does not always prevent progression of glaucomatous neurodegeneration.[5,12–14] Optic neuropathy in LPG presumably is related to risk factors other than just IOP. In the Collaborative Normal-Tension Glaucoma Study, the percent reduction in IOP did not correlate with the reduced rate of visual field progression,[11,12,15] and IOP was not significantly associated with progression in untreated eyes.[16] Possible IOP-independent mechanisms include vascular, structural, metabolic, autoimmune, or genetic defects and alterations in retinal ganglion cell survival pathways, including intrinsic molecular pathways or retrograde neurotrophin transport from the lateral geniculate nucleus. Laboratory research over the past decade has focused on the potential to manage glaucoma not only by lowering IOP, but also with treatment methods aimed at the vulnerable optic nerve itself.

In animal models of focal cerebral ischemia, α_2-adrenergic agonists have a neuroprotective effect.[17] Systemic administration of the selective α_2-adrenergic agonist brimonidine has been shown to protect the optic nerve and retinal ganglion cells from secondary degeneration after a partial crush injury to the adult rat optic nerve[18,19] and to protect retinal ganglion cells in the ocular hypertensive rat model.[20] Topical administration of brimonidine results in pharmacologically therapeutic concentrations of drug in the vitreous in laboratory animals[21,22] and humans.[23] Topical ocular dosing with brimonidine therefore is believed to provide a route for drug delivery to the retina in amounts sufficient to bind and activate the α_2-adrenoceptor. In this way, brimonidine could function to maintain the health of the optic nerve. This assertion has not been proven in clinical glaucoma trials.[24] Because the ocular hypotensive efficacy of brimonidine tartrate 0.2% and timolol maleate 0.5% are similar in monotherapy,[25–27] any treatment benefit in eyes receiving brimonidine compared with eyes receiving timolol may support an IOP-independent (i.e., neuroprotective) mechanism of action.

The Low-Pressure Glaucoma Treatment Study (LoGTS) is the first large, double-masked clinical trial comparing the course of LPG patients randomized to IOP reduction with topical twice daily brimonidine tartrate 0.2% versus twice daily timolol maleate 0.5%. This article presents the study protocol and baseline characteristics of study participants.

Patients and Methods

The LoGTS is a multicenter, randomized clinical trial testing the null hypothesis that no differences in visual field stability or progression will occur among LPG patients randomized to treatment with brimonidine compared with those randomized to treatment with timolol. Secondary aims include the evaluation of IOP and optic disc morphologic changes by treatment groups over time. The LoGTS also will explore factors that may influence progression in LPG using generalized linear models, such as logistic regression on predictive variables for progression in the 2 groups. Table 1 presents the major study design features.

Study Organization

The LoGTS organization consists of 13 clinical centers. The study protocol and informed consent were approved by Institutional Review Boards at all participating centers. A Data Center for masked computer analysis of the visual fields is located at University Eye Specialists, Chicago, and a Data Center for the optic disc photographs is located at University Eye Specialists, Chicago, and the Hamilton Glaucoma Center of the University of California, San Diego. The randomization assignment list is maintained and masked study medications are provided directly to the clinical centers by Fountain Valley Pharmacy (Fountain Valley, CA). Optic disc, visual field, and coordinating centers are masked from each other. Data on treatment effects and the randomization code are not provided during the course of the study. The study is supported by an unrestricted grant from Allergan, Inc. (Irvine, CA) to the Low-Pressure Glaucoma Study Group and the Chicago Center for Vision Research (Chicago, IL).

Eligibility Criteria

The diagnosis of LPG required open iridocorneal angles by gonioscopy and glaucomatous visual field defects in at least 1 eye on Humphrey 24-2 full-threshold standard automatic perimetry. At least 2 visual field examinations with acceptable reliability standards (fixation loss <33%; false-positive rate <33%; false-negative rate <33%) were required within the prior 6 months. Criteria of visual field abnormality were the presence of at least 3 contiguous points depressed more than 8 decibels or 2 contiguous points depressed more than 10 decibels. Location and pattern of the defect had to be consistent between the prestudy fields. The appearance of the optic disc had to be consistent with the visual field damage. Inclusion and exclusion criteria are listed in Table 1.

Sample Size and Power Analysis

A sample size was selected to provide sufficient statistical power (at least 80%) to detect outcome differences between the 2 study groups based on the following premises: (1) a 4-year visual field progression rate of 55%[28] in the timolol group and assuming a 30% progression rate in the brimonidine group (sample size is