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Early Manifest Glaucoma Trial (EMGT)[1,2]

Reviewed by Patricia M. Khu, MD, MS

STUDY SUMMARY

Enrolled were 255 patients aged 50 to 80 years (median, 68 years) with early glaucoma defined as follows:

- Newly detected, previously untreated primary open-angle glaucoma, normal-tension glaucoma, or exfoliation glaucoma;
- Reproducible glaucomatous visual-field defects (Humphrey 24-2 full threshold) in at least one eye.
- Mean deviation (MD) ≤10 dB in at least one eye and no threat to fixation ≥ 10 dB at test points closest to point of fixation);
- Visual acuity ≥0.5 (20/40 or 6/12) in any eye;
- Mean IOP ≤ 30 mm Hg and no IOP > 35mm Hg in any eye.

Eligible patients were randomized evenly as control (n=126) and treatment (n=129) groups. All eyes randomized to treatment received a full 360º trabeculoplasty plus betaxolol 0.5% (Betoptic 0.5%, Alcon, Forth Worth, TX, USA) twice daily. Study visits included visual-field tests and tonometry every 3 months, and optic-disc photography every 6 months. Latanoprost 0.005% (Xalatan, Pfizer, NY, NY, USA) once daily was added if IOP after 2 consecutive follows-ups exceeded 25mm Hg in the treatment group and 35mm Hg in the control group.

Patients stayed in their allocation arms unless significant progression occurred, defined as either of the following:

- Visual-field progression: 3 or more test-point locations showing significant deterioration from baseline in glaucoma change probability maps from 3 consecutive tests;
- Optic-disc progression: determined by masked graders using flicker chronoscopy plus side-by-side photogradings.

After a median follow-up period of 6 years, treatment reduced the IOP by 5.1 mm Hg or 25%, which was maintained throughout follow-up. Progression happened less frequently in the treatment group (58/129; 45%) than in the control (78/126; 62%) ($p = 0.007$) and occurred significantly later in treated patients (66 months v. 48 months in control). Progression varied across patient categories, but treatment effects were present in both older and younger patients, high- and normal-tension glaucoma, and eyes with less and greater visual-field loss. These effects were greater with longer follow-up.

In multivariate analyses using median values, treatment halved the risk for progression (HR=0.50; 95% CI, 0.35-0.71). Predictive baseline factors for progression were higher IOP (HR=1.70), exfoliation (HR=2.31), involvement of both eyes (HR=1.93), worse MD (HR=1.55), and older age (HR=1.43). Using continuous values, the risk of progression increased by 5% with each mm Hg of higher baseline IOP (HR=1.05; 95% CI, 1.01-1.10), by 3% per 1dB of worse MD (HR=1.03; 95% CI 0.98-1.09), and by 1% per 1 year of age (HR=1.01; 95% CI, 0.98-1.05). Progression risk decreased by about 10% with every mm Hg of IOP reduction from baseline to first follow-up visit (HR=0.90; 95% CI 0.86-0.94).

COMMENTS

The EMGT is a well-conducted randomized, controlled clinical trial evaluating the effectiveness of reducing IOP in patients with newly detected, previously untreated early glaucoma. It has a control arm in which patients underwent follow-up without treatment as long as progression did not occur. The two groups have the same number of participants, similar rates of follow-up, and low attrition rates (2.4%).

There was no selection bias; eligible patients were randomized evenly between the groups according to a permuted block randomization scheme stratified by the clinical and satellite centers. Data on both visual-field and optic-disc outcomes were obtained by masked observers. The visual-field criterion used was based on previously tested statistical programs for visual-field analysis and was numerical and objective. The glaucoma-change probability maps were based on pattern deviation rather than total deviation, strongly reducing any confounding effects of progressing lens opacities on visual-field outcomes.[3] Moreover, the criterion for visual-field progression was defined at the start of the trial and was not changed during the study.

The EMGT perimetric criterion has high sensitivity and was able to detect visual-field changes earlier than other measures of progression.[4-5] In this study, the progression of glaucoma was determined principally by using the visual-field criterion, either alone or with corresponding optic-disc findings. Only one patient in the treatment group had progression based solely on optic-disc changes. The inclusion of both criteria

independent of each other and the stringent manner by which progression was assessed made possible the detection of definite early glaucomatous changes, even in the absence of modern perimetric methods of assessing early functional changes (frequency doubling perimetry or short wavelength perimetry), or methods of quantifying morphologic changes in the optic-nerve head and retinal nerve-fiber layer (retinal tomography, scanning laser polarimetry or optical coherence tomography). The EMGT criteria for progression were applied equally to both groups by outcome assessors who were masked as to the treatment assignment of each patient. Even though the patients and the treating physicians were not masked, the study personnel measuring the visual acuity, IOP, and visual fields were masked to patients' study group. Hence, those obtaining study outcomes were unaware of the study grouping of each patient and the results recorded were therefore not biased.

To remove the effect of compliance to glaucoma medications, the standard treatment used in this study included laser trabeculoplasty (LTP) in addition to a glaucoma medication. This was to avoid fluctuating IOP over the period of observation. LTP provides temporary but good IOP reduction and can be used either to supplement glaucoma medications or as first-line treatment.[6]

Study limitations

The patients were recruited during a population screening and data obtained could only be extrapolated to the general population. Moreover, the study involved a specific, homogenous patient population of white individuals and may not be applicable to other ethnic groups whose glaucoma progression may be different. Patients in this study also had relatively early glaucoma with IOP no greater than 30 mm Hg and mild visual-field defects, so the study results cannot provide quantitative data pertaining to patients with IOP levels greater than 30 mm Hg, or to those with advanced visual-field loss. Once progression was determined in patients of either group, glaucoma medication was added. This shortened the ascertainment of the natural history of glaucoma.

The EMGT only studied the beneficial effects of IOP lowering and did not study other risk factors (non-IOP risk factors) that may play a role in glaucoma progression.

IMPLICATIONS ON CLINICAL PRACTICE

In the era of evidence-based medicine, the EMGT is the first randomized study providing a long-term comparison of progression between treated and untreated patients with early glaucoma. The results not only confirm previous beliefs that IOP reduction is beneficial but also provide new knowledge on rates of disease progression, with and without treatment, in patients with various characteristics. The results also support the need for early detection and treatment of glaucoma to prevent blindness.

The time to progression varied greatly among treated and untreated patients in this study, indicating that there were different rates of progression for different patients and different responses to the same treatment regimen. In the treatment group, either there was inadequate IOP control in those who progressed or there were other risk factors present (non-IOP risk factors) that played a major role in the progression of the disease. This demonstrated that a standard treatment regimen was insufficient to prevent progression in all glaucoma cases, specifically in those where the disease process was more rapid. In the "no treatment" group, many also showed no progression after six or more years of follow-up. Thus, the treatment regimen should be individualized for each patient, taking into consideration the presence of different risk factors. Careful follow-up may allow deferment of treatment in some patients until the rate of disease in the particular individual has been established over a period of observation.

How relevant are the results of the EMGT study to our clinical practice? One way is to look at the measures of treatment effect as follows:

Progression	Control	Treatment
Baseline risk	61.9%	45.0%
Relative risk (RR)		0.73
Relative risk reduction (RRR)		0.27
Absolute risk reduction (ARR)		16.9%
Number needed to treat (NNT)		6

The baseline risk for progression in the "no treatment" group is approximately 62% and in the treatment group 45%. The relative risk (comparing treatment to control) is 73% and the relative risk reduction (opposite of RR) is 27%. The absolute risk reduction is almost 17%, obtained by subtracting baseline risk of treatment group from that of control group. Getting the inverse of ARR is the number needed to treat to see the immediate effect of treatment. The NNT is small if the baseline risk is high and large if the baseline risk is low. In this study, for every 6 patients undergoing glaucoma treatment, progression is prevented in one patient. This is highly significant since its beneficial effect is seen in treating just six patients. This clearly indicates that *every* patient with early glaucoma should undergo treatment to prevent progression of the disease.

The EMGT study also supports the contention that the lower the initial IOP reduction in early glaucoma, the lower the risk of progression. For every 1 mm Hg decrease in the IOP on follow-up, there is an approximate 10%

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