

The articles that follow are part of an ongoing series that aims to review collaborative prospective studies supported by the National Eye Institute. The first article, written by investigators, will remind readers of the rationale, goals, methods, findings, and recommendations. The second article, written by an expert who did not participate in the investigations, will offer a constructive critique and attempt to estimate the impact of the study on the practice of ophthalmology.

Ocular Hypertension Treatment Study

Eve J. Higginbotham, MD

FOR DECADES BEFORE THE INITIATION OF THE Ocular Hypertension Treatment Study (OHTS),¹ no consensus existed among ophthalmologists regarding the treatment of patients with ocular hypertension. Some studies²⁻⁶ affirmed the protective benefits of treatment, and other studies⁷⁻¹² did not support the use of preventive medical therapy. Therefore, it was unclear if early treatment was beneficial. Most of these studies did not enroll a diverse patient population,²⁻¹² others used a single medication as an intervention,^{2,3,5,6,10} and all differed in their definitions of glaucoma. Moreover, questions were raised by health outcomes experts outside the field of ophthalmology regarding whether treatment of glaucoma in general was beneficial.¹³ Thus, a well-designed clinical trial was needed to assist clinicians in determining whether treatment is protective and, if so, which patients would benefit most from treatment.

METHODS

What were the primary objectives and study design of the OHTS? The 2 primary study objectives were (1) to determine the safety and efficacy of topical ocular medication in delaying or preventing the development of primary open-angle glaucoma in individuals with ocular hypertension and (2) to determine the factors that predict which patients with ocular hypertension will develop primary open-angle glaucoma. Eligible patients were between the ages of 40 and 80 years and had an intraocular pressure (IOP) between 24 and 32 mm Hg in one eye and 21 and 32 mm Hg in the other eye. Given the high prevalence of glaucoma among African Americans, 25% of the participants enrolled were self-reported African Americans. Participants were randomized to topical medication or observation. The goal in the medication group was a 20% reduction of IOP and an IOP of less than 24 mm Hg. Clinicians could choose any commercially available topical medication to try to reduce IOP. All patients were followed up with perimetric tests and stereoscopic optic disc photography. The primary end point of glaucoma was defined as either a reproducible visual field abnormality or a reproducible, clinically significant change in the optic nerve.

Author Affiliations: Department of Surgery, Morehouse School of Medicine and the Department of Ophthalmology, Emory School of Medicine, Atlanta, Georgia.

Change was judged independently by masked readers at the Visual Field Reading Center (University of California at Davis or Sacramento, California) and the Optic Disc Reading Center (Bascom Palmer Eye Center, University of Miami, Florida). An end point committee, which consisted of masked clinicians, independently judged whether the changes were caused by primary open-angle glaucoma.¹

RESULTS

The importance of the characterization of the end points cannot be overemphasized, considering the imprecision of diagnosing glaucoma in clinical practice. Initially, the investigators agreed on a requirement of 2 consecutive perimetric tests to confirm a functional defect; however, analysis of this definition revealed that 85.9% of abnormalities initially detected were not confirmed on the next test.¹⁴ Therefore, 3 consecutive perimetric tests were required for an end point for the remainder of the study. A subsequent review of those end points based on 2 fields vs 3 fields confirmed the wisdom of this change in protocol.¹⁵ When considering the precision of characterizing the optic disc, the Optic Disc Reading Center reported exceptional reproducibility when horizontal cup-disc ratios were determined during a 3-year period.¹⁶ These same investigators later demonstrated a high level of consistency in their ability to detect deterioration in the optic disc appearance over time.¹⁷ Both functional and structural measures proved to be important, considering that 41 of 168 eyes reached an end point based on both visual field abnormality and optic disc deterioration, 40 of 168 eyes on visual field abnormality alone, and 87 of 168 eyes on optic disc deterioration alone.¹⁸

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What was the primary outcome of the study? Patients treated with medication were less likely to develop glaucoma during a period of 60 months compared with those who were simply observed: 4.4% of the medication group patients developed primary open-angle glaucoma vs 9.5% of the observation group patients.¹ Among self-reported African Americans, 8.4% of the medication participants converted to glaucoma vs 16.1% in the observation group. Compared with all

other ethnic groups taken together, the conversion rate for African Americans was 200% greater in the medication group and 58% greater in the observation group.¹⁹ The benefits of medical therapy and the difference in disease progression in different ethnic groups in a diverse cohort were not previously documented in a randomized trial. The design of the study and the quality of the measures chosen for the end points provide a level of certainty that the results are valid and translatable to clinical practice.

The goal of reducing IOP was achieved among the treated eyes, with a mean (SD) reduction of 22.5% (9.9%) vs 4.0% (11.6%) in the observation group.¹ No difference was found in the response to therapy among self-reported African Americans compared with others²⁰; however, a difference in the measured IOP response to topical therapy was noted among those with thinner corneas vs thicker corneas.²¹ Moreover, not surprisingly, among those individuals who started taking a β -blocker, 45% of the untreated contralateral eyes demonstrated a reduction in IOP of 3 mm Hg or more.²² When considering the question of safety, a greater proportion of individuals in the medication group reported symptoms such as dryness, tearing, and itching compared with those in the observation group.¹ Little difference was noted between the medication group and the observation group in overall adverse events and serious adverse events. Among those participants randomized to medication, there was a slightly higher rate of cataract surgery in the medication group, but no apparent overall impact was seen on either lens opacification or visual function.²³ Severe psychiatric and genitourinary adverse events were slightly more common in the medication group.¹

The analysis of baseline demographic and clinical data provided the most effective vehicle for the OHTS to ultimately influence clinical practice. Gordon and coworkers²⁴ identified several key baseline factors predictive of primary open-angle glaucoma: older age, higher IOP, larger vertical cup-disc ratio, a higher pattern standard deviation on visual field testing, and thinner corneal measurement. After an analysis of the baseline factors among the self-reported African Americans in the study, ethnicity proved to not be a significant risk factor when adjustments were made for key parameters, such as larger cup-disc ratio and thinner corneal measurement.¹⁹ The presence of a disc hemorrhage was associated with an increased risk of developing glaucoma, with a 3.7-fold increased risk in a multivariate analysis.²⁵ Among a subset of patients who were followed up with confocal laser ophthalmoscopy, a number of baseline indices were significantly associated with the development of glaucoma.²⁶ As a further testimony to the validity and relevance of the OHTS to other populations, a prediction model was developed based on the observation group of the OHTS and then subsequently tested on the placebo group of the European Glaucoma Prevention Study.²⁷ This additional analysis confirmed the same predictors for developing primary open-angle glaucoma as did the original model reported by the OHTS.

The authors of the OHTS appropriately concluded that not everyone with ocular hypertension should be treated; treatment should be considered for patients at moderate

to high risk for developing primary open-angle glaucoma. A clinician must consider a patient's risk of developing primary open-angle glaucoma, as well as the patient's health, life expectancy, and personal preferences. A cost-utility analysis of the OHTS data supports the early treatment of those individuals with an IOP of 24 mm Hg or higher and a 2% or greater annual risk of developing glaucoma and reaffirms that the treatment of all patients with ocular hypertensives is not cost-effective.²⁸ These observations are the most significant products of this multicenter randomized clinical trial.

COMMENT

The OHTS has yielded a wealth of useful clinical information, which will guide the management of individuals with ocular hypertension for decades to come. Not only did this study provide a definitive basis for managing patients with ocular hypertension but also the profession has benefited by lessons learned in the study related to optic disc assessment, analysis of perimetric test findings, and corneal thickness measurements. Until clinicians have the benefit of specific genetic profiles for patients to guide their clinical decisions, they can be guided by measurable biological risk factors (ie, thin central corneal measurement, large cup-disc ratio, increasing age, abnormal visual function, and higher IOP) to determine which patients should be considered for early treatment.

Submitted for Publication: December 21, 2007; final revision received January 8, 2008; accepted January 9, 2008.

Correspondence: Eve J. Higginbotham, MD, Department of Ophthalmology and Visual Science, Morehouse School of Medicine, 720 Westview Dr, Atlanta, GA 30310 (ejhigginbotham@msm.edu).

Financial Disclosure: None reported.

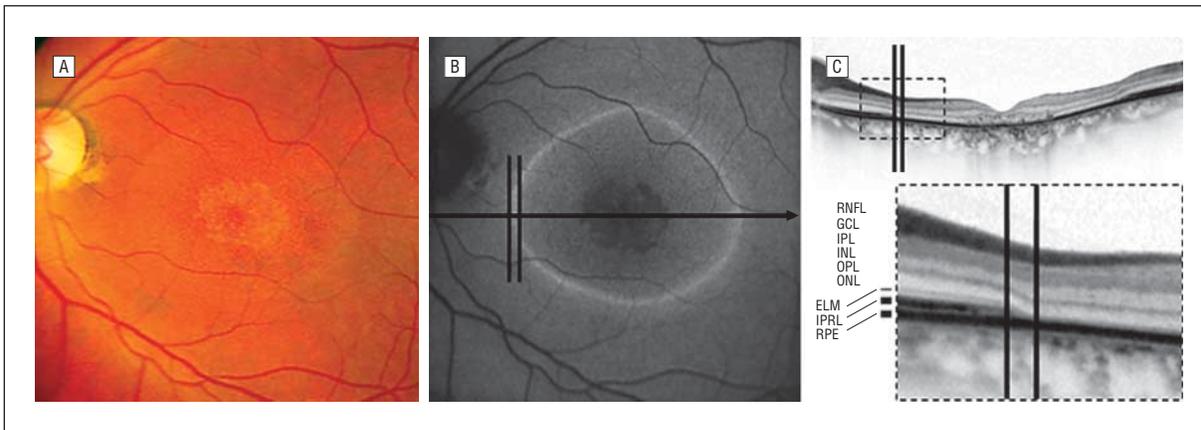
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Archives Web Quiz Winner

Congratulations to the winner of our September quiz, Theodore K. Lin, MD, Vitreoretinal Fellow, Department of Surgery, Section of Ophthalmology and Visual Sciences, University of Chicago, Chicago, Illinois. The correct answer to our September challenge was pigmented paravenous retinochoroidal atrophy. For a complete discussion of this case, see the Small Case Series section in the October *Archives* (Fleckenstein M, Issa PC, Helb H-M, Schmitz-Valckenberg S, Scholl HPN, Holz FG. Correlation of lines of increased autofluorescence in macular dystrophy and pigmented paravenous retinochoroidal atrophy by optical coherence tomography. *Arch Ophthalmol.* 2008;126[10]:1461-1463).



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