Ocular Hypertension Treatment Study (OHTS) commentary

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Purpose of review

To summarize the major findings of the Ocular Hypertension Treatment Study (OHTS).

Recent findings

Ocular hypertensive subjects who received topical glaucoma medication experienced conversion to glaucoma at less than half the rate of subjects who were monitored without treatment. Risk factors for converting to glaucoma included older age, higher intraocular pressure, larger cup-disc ratio, higher pattern SD, and thinner central corneal thickness.

Summary

The OHTS clearly established that medically treating ocular hypertension is efficacious in delaying or preventing the onset of glaucoma. Further, the results may assist in providing useful guidelines for determining who with ocular hypertension should be offered medical treatment.

Keywords

Ocular hypertension, primary open-angle glaucoma, glaucoma risk factors, glaucoma incidence.

Curr Opin Ophthalmol 14:74–77 © 2003 Lippincott Williams & Wilkins

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Current Opinion in Ophthalmology 2003, 14:74–77

Abbreviations

CCT	central corneal thickness
C/D	cup-to-disc
IOP	intraocular pressure
OHTS	Ocular Hypertension Treatment Study
PSD	greater pattern SD
SWAP	short-wavelength automated perimetry

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About the Ocular Hypertension Treatment Study (OHTS)

Background

The Ocular Hypertension Treatment Study (OHTS) is a multicenter, randomized clinical trial designed to determine the efficacy of topical ocular hypotensive medication in delaying or preventing the onset of glaucoma in patients with ocular hypertension. This study was funded by the National Institutes of Health (NIH) for a 5-year period beginning in September 1992. Administrative renewal was awarded December 1998 through November 2003. The original study aims were achieved and published in companion papers in June, 2002. One paper established that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma [1•]. The other paper reported on baseline factors that predict the onset of primary open-angle glaucoma [2•].

Design

After screening over 3000 potential participants, 1636 individuals were found eligible for entrance into the trial. Following are key inclusion criteria that apply to both eyes of study individuals: presence of ocular hypertension, defined as an intraocular pressure (IOP) between 24 mm Hg and 32 mm Hg in one eye and between 21 mm Hg and 32 mm Hg in the other eye; normal optic nerve function and structure, as ascertained by two reliable 30–2 Humphrey visual fields per eye and by stereoscopic disc photographs; age between 40 and 80 years. Individuals could not have had prior intraocular surgery other than uncomplicated cataract surgery and could not have any condition with a potential of causing field loss, such as diabetic retinopathy.

Eligible participants were randomly assigned to either a group treated with topical ocular hypotensive medications or to a group simply observed without ocular hypotensive treatment. Individuals randomized to topical ocular hypotensive therapy began treatment to achieve an IOP of 24 mm Hg or less and a minimum 20% reduction from the average of the qualifying IOP and the IOP at the visit at which the randomization group was assigned. Medication was changed or added until both of these goals were met or until the patient was receiving maximally tolerated medical therapy. Providers were free to prescribe any commercially available topical agent to the patients in the treatment arm of the study. Follow-

up clinical examinations were made every 6 months. Visual fields were obtained every 6 months and stereoscopic disc photographs were obtained every 12 months; these were sent to the OHTS Visual Field Reading Center or the OHTS Optic Disc Reading Center, respectively.

The primary outcome measure was the development of glaucoma in one or both eyes. Either a glaucomatous change in the visual field or a glaucomatous change in the appearance of the optic nerve qualified as conversion to glaucoma. An abnormality in the visual field was defined as $P < 0.05$ for the corrected pattern SD or a Glaucoma Hemifield Test result "outside normal limits." Deterioration in the optic disc was defined as a generalized or localized thinning of the neuroretinal rim compared with baseline stereoscopic disc photographs. A stringent two-layer review system was put in place to confirm any possible glaucomatous conversion. Masked certified readers at the OHTS Visual Field Reading Center or at the OHTS Optic Disc Reading Center requested confirmatory visual fields or photographs when a change was suspected based on these established criteria. Confirmed changes were then reviewed in a masked fashion by the Endpoint Committee to verify and declare a glaucomatous conversion.

Commentary

The OHTS study design has many strengths, including a large sample, strictly applied enrollment protocols, careful determination of endpoints, and prospective, longitudinal assessments which yield incident cases of glaucoma. There are also some limitations that should be kept in mind. Although OHTS used a conventional definition of ocular hypertension as an entry criterion, thereby supporting applicability to current clinical practice, those who qualified were likely more "normal" than typical ocular hypertensive subjects in clinical practice. The issue of appropriately defining "ocular hypertension" in light of technological advances in diagnostic tools must also be addressed.

Numerical values can be used to define one cornerstone of ocular hypertension (namely IOP), but no definition exists for another cornerstone of the condition (namely a nonglaucomatous optic nerve). To be eligible for entry into the OHTS, patients had to have normal structure and function of the optic nerve. What is normal structure? No specific eligibility criteria were described, although grossly evident features such as disc hemorrhage or focal tissue loss were undoubtedly deemed ineligible by the Reading Center. What is normal function? It may not merely be normal performance on standard achromatic automated perimetry. It has been proven that alternative perimetric tests, notably short-wavelength automated perimetry (SWAP), presage conventionally determined glaucomatous visual field deficits by being more sensitive in detecting compromised optic nerve function. For this reason, an OHTS ancillary study using SWAP is currently being performed on a sample of the OHTS patients in selected centers.

As discussed later, examination of the OHTS database using a time-series model shows increased risk of conversion in optic nerves with higher pattern SDs and cup-to-disc ratios, possibly signifying preexisting glaucomatous damage to these nerves. Analysis of data compiled by the Ancillary Study Reading Centers of the OHTS, which involve assessment of the study population using digital imaging technology and SWAP, may be illuminating in this regard. Findings may emerge that refine the definition of ocular hypertension and, ultimately, may enhance the applicability of the OHTS to clinical practice.

Primary finding and commentary

Finding

The specific objective of the OHTS was to determine the efficacy of topical medication in reducing the risk of developing glaucoma among patients with ocular hypertension. The overall IOP of the treated population was decreased by an average of 22.5% and the overall IOP of the observed population was decreased by an average of 4.0% over the course of the study. The recently published primary endpoint paper showed that after 60 months of treatment, the cumulative probability of developing glaucoma was 4.4% in the treated group and 9.5% in the untreated group [1•].

Commentary

The OHTS affirms the hypothesis that topical ocular hypotensive medication can delay or prevent the onset of glaucoma in patients with ocular hypertension. Together with information culled from three other large prospective clinical trials, the primary findings of the Normal Tension Glaucoma Treatment Study and the Early Manifest Glaucoma Treatment Study and an ancillary finding of the Advanced Glaucoma Intervention Study, the OHTS supports the clinical impression that reduction of intraocular pressure serves as neuroprotection to an optic nerve susceptible to glaucoma.

However, it is imperative that providers digest the results of the primary results of the OHTS carefully. The OHTS does not impart firm clinical guidelines for providers, either about whether to treat or how to treat. The decision whether to treat requires the integration of patient-centered concerns, which includes weighing the relatively small likelihood of actually developing visually symptomatic pathology against the burden of long-term treatment. Indeed, of the study participants who converted to glaucoma, over half converted on the basis of optic disc structural changes alone, without any visual field loss. Furthermore, over the course of 5 years, the

probability of developing glaucoma in the treated population was halved, but was nonetheless only 5% above baseline. Additionally, while the OHTS safety and quality-of-life outcomes suggested no evidence of significant adverse medical effects from treatment, it is difficult to evaluate the economic and psychological costs of treatment of patients who are not part of a clinical study. Finally, the prognosis of a patient who delays therapy until converting to glaucoma is unknown. These caveats about whether to initiate treatment, though, should be placed in proper perspective. In particular, the disparity in conversion rates between treated and untreated patients is likely to be greater over a time period longer than 5 years. Some guidance may also be offered by findings published in the companion paper to the OHTS results, as will be discussed later.

Should treatment be started, the OHTS does not provide management guidelines on how to treat. No choices of drug, optimal target pressure, or appropriate follow-up schedule are indicated by the OHTS. The OHTS protocol gave each investigator freedom to choose any commercially available topical drug, including the most recent class of agents, the prostaglandin analogues. The study design achieved its arbitrarily chosen goal of a 20% reduction in IOP; while reasonable to believe, it is nevertheless unknown whether a more aggressive reduction target would have further lowered the conversion risk. Finally, while all study patients in OHTS received examination, visual field testing, and optic disc photography at reasonable time intervals, it cannot be presumed that these follow-up intervals are optimal for management of all patients with ocular hypertension in clinical practice.

Ancillary finding and commentary

Finding

The massive OHTS database afforded the opportunity to determine some demographic and clinical factors associated with conversion to glaucoma from simple ocular hypertension. The companion paper to the primary OHTS publication revealed that older age, larger cup-to-disc (C/D) ratio, greater pattern SD (PSD), higher intraocular pressure, and thinner central corneal thickness (CCT) appear to be good predictors for development of glaucoma in patients with ocular hypertension. These factors were used in combination with each other to separate patients to low, moderate, and high risk of developing glaucoma. Family history was not found to be significant in either the univariate or multivariate analysis, and race (black) was significant in the univariate but not in the multivariate analysis.

Commentary

In demonstrating the existence of demographic and clinical factors that are important in the development of glaucoma, certain management guidelines for providers caring for patients with ocular hypertension are suggested. Data were gathered about certain patient characteristics because they may stratify the risk for conversion to glaucoma, which may be helpful when considering whether to initiate treatment to delay or prevent glaucoma. The OHTS database identified age, C/D ratio, and IOP as important factors. These data are usually acquired in general clinical practice. PSD was also identified as being an important factor. However, its real world significance is deemed questionable by the fact that a given patient's PSD can vary widely because the value arises from a proprietary statistical program assessing a psychophysical parameter. Finally, multivariate analysis on the database identified the importance of CCT as a predictor. This measurement is not routinely acquired in most clinical practices. The strength of CCT as a predictor for conversion to glaucoma over the range of IOP values and cup-disc ratios suggests that the measurement of CCT should be an essential element to a standard workup of patients with ocular hypertension. One of the ancillary publications of the OHTS [3] provides detailed data on baseline CCT measurements and discusses the association between CCT and IOP measurements.

The mechanism by which CCT exerts its risk for glaucoma is unknown. One possibility is that it is operating through IOP. Thinner corneas will have lower measured applanation IOP readings than the actual IOP and thicker corneas will have higher measured readings than the actual. Thus, the higher risk of conversion to glaucoma with thinner corneas may be because these eyes have higher actual IOP than measured. On the other hand, the risk of CCT may be through a mechanism entirely independent of IOP.

Of particular interest is the lack of significance of race and family history of glaucoma, both of which are commonly assumed to be important glaucoma risk factors. That family history was not found to be significant is explainable by the fact that the presence or absence of family history was by patient self-report. Many patients are not knowledgeable of their family history, while many others mistake a number of other eye conditions for glaucoma. The likelihood of misclassification with this variable is thus quite high. That race was significant with univariate but not with multivariate analysis suggests that race as a risk factor is operational through one or more other variables. For example, black patients have thinner central corneas and larger cup-disc ratios than white patients, and both of these factors are associated with increased risk.

Also of interest is that comorbidity with diabetes was found to be protective against developing glaucoma. Although the evidence for diabetes being a risk factor for glaucoma is not nearly as strong as for race or family

history, a protective effect of diabetes is counterintuitive. However, the study did not medically verify the self-report of diabetes and it excluded patients with diabetic retinopathy. The trial therefore enrolled an unrepresentative and unconfirmed sample of diabetics and the results related to diabetes is considered to be unreliable.

Data from OHTS were carefully collected and analyzed and the results offer many important findings. As with any study, the results must be critically interpreted from a statistical perspective. The database was analyzed with a time-series Cox proportional hazards model, which has certain features that need to be understood. Employment of this time-to-event modeling approach afford the opportunity to extract more information from the data than would have been obtained by merely condensing the data by performing a standard regression analysis at the end of the trial time period. The time-series method, then, captures a sense for how the factors influence the rate of change to glaucoma from ocular hypertension, as opposed to just the likelihood of change. Appropriate application of this approach assumes, for one, a well-defined entry point because modeling depends on length of time to an endpoint to determine the rates. However, this assumption is violated in the OHTS because the length of exposure of patients to ocular hypertension was unknown. Quite possibly, this violation may be manifested in the finding of the predictive nature of older age, higher PSD, and higher C/D in developing glaucoma since optic nerves with such features may already have undergone some form of subtle glaucomatous damage from long exposure to ocular hypertension.

Conclusions

The OHTS decisively achieved its primary aim to demonstrate the effect of reducing intraocular pressure in the context of ocular hypertension. The results clearly reveal a relation between ocular hypertension and the development of glaucoma. Over the course of 5 years, a 20% reduction in IOP led to an approximate two-fold rate of reduction in conversion to glaucoma. The strength of the study design of OHTS confidently certifies the validity of this scientific evidence.

Clinical medicine, however, is still an art, and the strong biologic evidence presented by the OHTS cannot answer for the clinician the question of whether a particular patient with ocular hypertension should be treated. The decision whether to treat requires incorporating patient-centered concerns about the value of treatment with the scientific findings about the effect of treatment. The OHTS data provide some useful clues to which patients are at highest risk and most likely to benefit from treatment. While statistical issues need to be carefully considered, factors that appear positively associated with glaucomatous conversion include older age, higher IOP, larger C/D ratio, greater PSD, and thinner CCT.

The true worth, ultimately, of the OHTS is that it offers the clinician quantitative evidence to begin an informed dialogue with an individual with ocular hypertension. Further revelations emerging from the remarkable OHTS longitudinal database promise to offer the clinician a better understanding about fundamental questions in glaucoma management, such as what constitutes glaucomatous optic nerve damage and the long-term destiny of vulnerable optic nerves—revelations that can serve only to further enhance the patient-physician dialogue.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 • Kass MA, Heuer DK, Higginbotham EJ, et al.: The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002, 120:701–713.

This is the primary outcome paper from OHTS. The safety and efficacy of topical ocular hypertensive medication in delaying or preventing the onset of POAG are presented.

2 • Gordon MO, Beiser JA, Brandt JD, et al.: The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002, 120:714–720.

This is the companion paper to the primary outcome paper and it examines risk factors for converting from ocular hypertension to primary open-angle glaucoma.

3 Brandt JO, Beiser JA, Kass MA, et al. for The Ocular Hypertension Treatment Study (OHTS) Group: Central corneal thickness in the Ocular Hypertension Treatment Study. Ophthalmol 2001, 108:1779–1788.