The Ocular Hypertension Treatment Study (OHTS)[1, 2]

Reviewed by Jose Ma. G. Martinez, MD

STUDY SUMMARY

A randomized clinical trial involving 22 clinical centers in the United States of America, the OHTS aimed to determine the safety and efficacy of topical hypotensive medication in delaying or preventing primary open-angle glaucoma (POAG) among ocular hypertensives. It also sought to identify predictive baseline factors for the development of POAG. The study population was mostly Caucasian (70%) and African American (25%); aged 40 to 80 years; IOP between 24 mm Hg and 32 mm Hg; and normal optic discs and visual fields. Randomized into treatment and control groups were 1636 participants. Target IOP reduction for the treatment group was 20% using a topical hypotensive agent.

The patients were followed up at regular intervals, with periodic visual-field testing and optic-nerve-head stereophotography for 5 years. The development of glaucomatous nerve damage and visual-field defects as evaluated by an independent masked committee using standard criteria were considered primary outcome measures.

During the course of the study, the mean IOP reduction was 22% in the treatment group and 4% in the observation group. The cumulative probability of developing POAG after 60 months was 4.4% in the medication group and 9.5% in the observation group (Hazard Ratio (HR)= 0.40; 95% CI, 0.27-0.59; $p < .0001$) a 46% reduction of risk. In multivariate analyses, the significant baseline predictive factors for POAG were thin central cornea (HR=1.71 per 40 micron disease), larger vertical cup-to-disc ratio (HR=1.32), higher pattern standard deviation (PSD) on standard achromatic perimetry (HR=1.27), and advanced age (HR=1.22). There was no significant difference ($p > 0.05$) in the rate of serious adverse events between the two groups. The authors concluded that topical hypotensive medication effectively delays or prevents the onset of POAG among ocular hypertensives.

COMMENTS

To date, the OHTS study has the largest sample size among all studies involving ocular hypertension. Eligibility criteria as well as end-point criteria were well defined using the most acceptable methods of stereophotography and automated achromatic perimetry. Although the subjects and clinicians were not masked, masked evaluators (glaucoma specialists) analyzed the main outcome measures. Patients in both groups had similar rates of dropouts, nonadherence to randomization, and subjects who completed the study. Patients were analyzed according to their randomization groups.

The study had several sources of selection bias. The subjects were generally healthy; few had debilitating systemic diseases. As a result, diabetes mellitus, shown to be a significant predisposing factor for glaucoma in other studies, was protective for the disease on multivariate analysis. The study was also selective of subjects who could do reliable perimetry and who had clear media for optic disc photography. The range of IOP studied was between 21 and 32 mm Hg. The study results can not provide quantitative data pertaining to patients outside of this IOP range.The risk of glaucoma damage increases exponentially (not linearly) with higher IOP above 30 mm Hg.[3] Thus, data in this study cannot be applied to patients with pressures above 32 mm Hg.

IMPLICATIONS ON CLINICAL PRACTICE

It is tempting to treat all ocular hypertensives given the large reduction of risk—50%. It is also easy to convince patients to take the side of "preventive" treatment with this figure. One only has to look at the whole picture to see that less than 15 % of patients in the study eventually developed glaucoma. The rarity of conversion to frank POAG is in keeping with other studies by Linner (34%, n=41)[4] and Armaly (1.7%, n=5886).[5] With a low event rate and little functional disability from the "disease" at its early stages, it is prudent to exercise caution in choosing whom to treat. The number needed to treat is 20 to prevent 1 patient from developing glaucoma. Treatment for all ocular hypertensives then becomes simply too costly for the benefit gained.

Most of the positive risk factors like age, larger CD ratio, and higher PSD are well known and have been validated by this study. Optic nerve head changes typically appear earlier than visual-field defects, and as such, close monitoring requires good optic-nerve evaluation.

The inclusion of CCT was the most interesting feature of the study. This represented a new, measurable factor that can strongly predict the development of POAG. Clinicians should definitely screen patients for thin corneas by doing pachymetry on all ocular hypertensives. As central corneal thickness obviously exerts its influence through errors in applanation measurements, doing pachymetry in all glaucoma patients may be justified.

The ultimate consideration, especially in economically challenged situations, is weighing costs against benefits. Costly treatment should be reserved for those who are sure to have the disease. Diligent follow-up becomes the key in managing ocular hypertension. This study shows clinicians how to conduct this follow-up and what to look for in each individual patient.