

# Answers From the Ocular Hypertension Treatment Study

**T**HE TREATMENT of ocular hypertension has been problematical in the few decades since it was recognized by Chandler<sup>1</sup> and Armaly<sup>2</sup> that only a minority of such patients were destined to develop glaucomatous damage.

On the conservative side, many glaucoma specialists advocate following such patients without treatment unless the intraocular pressure (IOP) is quite high (eg, 30 mm Hg)<sup>3</sup> or if it is difficult to be sure that the optic disc and visual field are normal. It is reasoned that observation alone allows timely intervention if damage begins, long before visual loss of consequence to the patient would occur, that in this way as many as 80% of patients with ocular hypertension avoid the cost and adverse effects of therapy, and that there is actually no convincing evidence that treatment delays or prevents damage.

## *See also pages 701 and 714*

On the other side of the debate, it is argued that up to 20% to 50% of the optic nerve fibers may be lost focally before damage is recognized by conventional perimetry<sup>4,5</sup> and that perhaps damage, once initiated, makes the remaining optic nerve fibers more susceptible to further damage. Furthermore, patients are more likely to be lost to follow-up if not treated,<sup>6</sup> and patients might blame the physician if substantial damage occurs before detection or if the first visual defect happens to be an annoying paracentral scotoma. Elevated IOPs also increase the risk of central retinal vein occlusion, which could cause sudden, irreversible visual loss.

While the academic community and textbooks generally take the side of withholding treatment, perhaps most general ophthalmologists in the United States and around the world treat anyone with a pressure greater than the low 20s or with risk factors such as black race or a family history of visual loss from glaucoma.

Finally, helpful guidance has arrived in the form of 2 landmark reports in this issue of the ARCHIVES. In the first, Kass et al<sup>7</sup> report the 5-year outcome of the Ocular Hypertension Treatment Study (OHTS) and clearly show that treatment is effective in delaying or preventing glaucomatous optic disc and/or visual field loss. Some 9.5% of controls and 4.4% of those treated developed confirmed damage.

In the study, 1636 higher-risk patients (IOP, 24-32 mm Hg) with ocular hypertension were randomized to either observation without treatment or to medical treatment. The goal of treatment was to reduce IOP to less than 25 mm Hg, with a minimum reduction of 20% re-

quired (except when <19 mm Hg). In actuality, a 22.4% reduction was achieved (mean, 24.9–19.3 mm Hg). However, since the controls were reduced by 4.0%, likely owing to regression to the mean, the true average reduction due to treatment was 18.4%, or 4.6 mm Hg.

In the companion report, Gordon et al<sup>8</sup> provide useful insight regarding the risk factors that identify those patients with ocular hypertension who are, and those who are not, at special risk for developing disc and/or field changes. The OHTS investigators were fortunate to have a biostatistician who is especially skilled at incorporating the nuances of clinical measurements in modeling disease.

The OHTS explored the role of central corneal thickness (CCT), which has been shown by others to make an artifactual contribution to IOP as measured by Goldmann applanation tonometry.<sup>9-11</sup> Correction factors of from -2.0 to -7.5 mm Hg/100  $\mu$ m above the population mean CCT have been suggested. In the OHTS, an increased CCT (>600  $\mu$ m) was noted in 27% of white patients and 14% of black patients.<sup>12</sup> In a previous report from OHTS,<sup>12</sup> it was estimated that (using the largest correction factor) up to 57% of white subjects and 37% of black subjects would have corrected IOPs in the normal range if adjustment were made for CCT. Now it is reported that subjects with increased corneal thickness of sufficient degree to account for much of their elevated IOP are indeed at rather low risk of developing glaucomatous damage. The investigators recommend that CCT be measured in all patients with ocular hypertension so that those patients who in reality do not have elevated IOP may be excluded from unnecessary surveillance.

Not surprisingly, those with higher baseline IOP and larger baseline cup-disc ratios had a greater risk of developing damage. For those with a mean baseline IOP of greater than 25.75 mm Hg, the risk of damage at 5 years was 36% in those with a thin or average cornea (<556  $\mu$ m) and 13% with a corneal thickness of 565 to 588  $\mu$ m, and for a cup-disc ratio greater than 0.3, the risk for those with a thin or average cornea was 24%; for those with a thickness of 565 to 588  $\mu$ m, it was 16%.

Clearly, the case for selective treatment of ocular hypertension has been strengthened by the demonstration of subgroups with a 24% to 36% risk of developing damage in 5 years, whereas previously the overall risk for progression of ocular hypertension was estimated to be 0.5% to 1.0% per year.

With the arrival of these reports from the OHTS, joining the results from other large clinical trials, the Collaborative Normal-Tension Glaucoma Study,<sup>13</sup> the Advanced Glaucoma Intervention Study,<sup>14</sup> and the Comparison of Initial Treatments of Glaucoma Study,<sup>15</sup> we

now have quite useful guidance on which to formulate treatment of glaucoma and ocular hypertension. In the high-risk normal-tension glaucoma patients,<sup>13</sup> a reduction of IOP from an average of 16 to 11 mm Hg resulted in a reduction in risk of progression (corrected for cataract) from 60% to 20%. In patients with primary open-angle glaucoma with moderate to severe visual field loss (mean, -10.5 dB at baseline), the mean visual field defect was related to the percentage of visits with an IOP of less than 18 mm Hg and to the mean IOP, with no net progression noted in 8 years of follow-up when at all visits the IOP was less than 18 mm Hg, at an average IOP of 12.3 mm Hg.<sup>14</sup> In patients with mild, initial damage (mean visual field defect, -5 dB), a reduction from 27 to 17 mm Hg (37% reduction) with medical therapy resulted in no average visual field progression over 5 years.<sup>15</sup> Now in the OHTS, the risk of developing glaucoma was reduced from 9.5% to 4.4% with an average 18% relative IOP reduction.

In each of these studies, there seems to be a dose-response relationship between IOP and the risk of visual field progression, with the curves shifting progressively to the right as one goes from normal-tension glaucoma to advanced primary open-angle glaucoma to mild primary open-angle glaucoma to ocular hypertension. Furthermore, in those instances in which we have details provided (all but the Comparison of Initial Glaucoma Treatments Study), a rough rule of thumb is that in the middle of each curve, a 3 mm Hg lowering of IOP corresponds to a 50% reduction in risk, as was reported for the entire population in the Baltimore Eye Survey.<sup>16</sup>

When the results of the Early Manifest Glaucoma Treatment Trial become available, all the pieces of the puzzle should be in hand, and hopefully an effort will be made to join the data sets and to use them to produce statistical packages on automated perimeters that, combined with other clinical data (IOP and CCT) and demographic information, will allow us to estimate the risk of glaucoma progression as a function of treated IOP. With such information, ophthalmologists and patients should be enabled to make better informed choices about treatment.

Kass and the OHTS investigators are to be congratulated for carrying out this important and well-conducted study.

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## REFERENCES

1. Chandler P. Long-term results in glaucoma therapy. *Am J Ophthalmol.* 1960; 49:221-246.
2. Armaly MF. Ocular pressure and visual fields: a 10-year follow-up study. *Arch Ophthalmol.* 1969;81:25-40.
3. Ritch R, Shields MB, Krupin T. Chronic open-angle glaucoma: treatment overview. In: Ritch R, Shields MB, Krupin T, eds. *The Glaucomas*. 2nd ed. St Louis, Mo: Mosby-Year Book Inc; 1996:1507-1519. Vol 3.
4. Quigley HA, Enger C, Katz J, Sommer A, Scott R, Gilbert D. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch Ophthalmol.* 1994;112:644-649.
5. Harwerth RS, Carter-Dawson L, Shen F, et al. Ganglion cell losses underlying visual field defects from experimental glaucoma. *Invest Ophthalmol Vis Sci.* 1999; 40:2242-2250.
6. Bigger JF. A comparison of patient compliance in treated vs untreated ocular hypertension. *Trans Am Acad Ophthalmol Otolaryngol.* 1976;81:277-285.
7. 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.
8. 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.
9. Whitaker MM, Stein RA, Hassanein K. The effect of corneal thickness on applanation tonometry. *Am J Ophthalmol.* 1993;115:592-596.
10. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol.* 2000; 44:367-408.
11. Ehlers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. *Acta Ophthalmol (Copenh).* 1975;53:34-43.
12. Brandt JD, Beiser JA, Kass MA, et al. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology.* 2001;108:1779-1788.
13. Collaborative Normal-Tension Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressure. *Am J Ophthalmol.* 1998; 126:487-497.
14. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS) 7: the relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol.* 2000;130:429-440.
15. Lichter PR, Musch DC, Gillespie BW, et al. Initial clinical outcomes in the Comparison of Initial Treatments of Glaucoma Study comparing initial treatment randomized to medicine or surgery. *Ophthalmology.* 2001;108:1943-1953.
16. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open-angle glaucoma among white and black Americans. *Arch Ophthalmol.* 1991;109:1090-1095.