

The Ocular Hypertension Treatment Study

Intraocular Pressure Lowering Prevents the Development of Glaucoma, but Does That Mean We Should Treat Before the Onset of Disease?

Editor's Note

The following articles suggest that there will be fewer patients receiving ocular antihypertensive medications based, in part, on applying the results of the Ocular Hypertension Treatment Study to clinical practice. Readers are invited to review these articles to see if they concur with the authors.

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WE WOULD LIKE to congratulate Kass et al¹ and Gordon et al² for their 2 well-written articles concerning a well-designed and important study. They clearly demonstrate that medical therapy that lowers intraocular pressure (IOP) prevents or retards the development of glaucoma in patients with ocular hypertension. This is noteworthy as it links the development of glaucoma to IOP lowering for the first time in a conclusive manner. This helps us better understand the glaucomatous process when combined with the results of other multicentered studies³⁻⁵ that find IOP lowering can retard the progression of glaucoma at various stages of the disease process.

The critical question is how to apply this information in clinical practice and policy making. Kass et al and Gordon et al find that medical treatment halves the development of the earliest detectable glaucoma damage given our current techniques. At 60 months, only 4.4% of treated patients compared with 9.5% of untreated patients develop glaucoma. If we look at one of the higher-risk groups, those patients whose IOPs were higher than 25.75 mm Hg and had corneal thicknesses less than 555 μ m had a 36% chance of developing glaucoma in 5

years without treatment.¹ Conversely, 64% of these relatively high-risk patients will not develop damage in a 5-year period. Kass et al then conclude that "clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG [primary open-angle glaucoma]."^{1(p701)} We believe that this recommendation requires further consideration.

Recent multicentered clinical trials have only dealt with a smaller proportion of the population that already has a disease. Intraocular pressure lowering in these people has been shown to retard glaucomatous progression in those afflicted. The Ocular Hypertension Treatment Study results affect a large percentage of the US population. The number of patients with ocular hypertension is large, and most of those will not develop visual-field loss. So, the issue is whether all these people should be treated.

Almost 8% (7.4%) of eyes have IOPs higher than 21 mm Hg on a single eye examination but do not have POAG as defined by optic nerve damage consistent with POAG.⁶ If we consider an IOP higher than 24 mm Hg, the proportion of the population without glaucoma is 3.5%. The implications of these Ocular Hypertension Treatment Study articles affect many patients and the

physicians who must make rational decisions based on the data in these articles. We must consider the benefits and costs of therapy, adverse effects of therapies, and quality of life issues before a plan of action is made.

Glaucoma is a serious, irreversible but slowly progressive disease.^{7,8} Because the disease affects the peripheral visual field first, it is usually many years from the onset of disease to functional visual loss unless the IOP is higher than the range studied in the Ocular Hypertension Treatment Study. Even using standard achromatic automated static perimetry, the physician can detect visual-field defects below the level of the defect from the physiologic blind spot, which we all live with and have no symptoms. Given the cost of treating all people with ocular hypertension at moderate to high risk of developing glaucoma, it may still be reasonable to wait until the earliest change in the optic nerve or visual field is detected.

Contrary to clinical perceptions, glaucoma progresses so slowly that most patients die before developing blindness, even in one eye. Quigley et al⁹ found that it takes 13 years for white individuals and 16 years for African American individuals to go blind from glaucoma. It appears to take 40 years for someone with visual-field loss at age 40 to become legally blind in one eye and develop visual-field loss in the fellow eye. In cross-sectional data using the Baltimore Eye Study,¹⁰ the Beaver Dam Eye Study,¹¹ and the Framingham Eye Study,¹² only 4% of white individuals and 8% of African American individuals with glaucoma are legally blind from it. Also, there is little evidence of an effect on health-related quality of life until the dis-

ease progresses to moderate or marked damage.¹³ Visual-field deterioration has also been shown to be slow, and functional loss associated with visual-field loss has been shown to be minimal until central vision is affected. In fact, Parrish et al¹⁴ found that only central vision correlated with health-related quality of life because peripheral visual-field loss from glaucoma was not a significant predictor of either global (Medical Outcomes Study 36-Item Short-Form Health Survey) or vision-specific (National Eye Institute Visual Functioning Questionnaire) quality of life measurements.

Glaucoma is not like cancer, which often, if caught at an early stage, is easier and cheaper to treat and more likely to yield a cure than if treated at a later stage when the disease can be fatal. Let us consider the consequences of treating patients with ocular hypertension. Let us assume that all who have no medical contraindications have tried taking timolol maleate, the standard medication that the Food and Drug Administration, Rockville, Md, uses as a gold standard to compare other IOP-lowering medications. The annual cost per patient, including an extra office visit to evaluate IOP-control timolol maleate gel, perimetry, and scanning laser ophthalmoscopy, is \$504. This is extremely expensive if treating a hypothetical population of 100 000 patients with ocular hypertension. Considering relevant mortality rates (to age 85 years) and assuming that annual rates of progression to POAG observed during the 5 years of the study continue for 35 years, that only those who are not blind are receiving physician visits, that only those who have not had incident POAG are receiving pharmaceutical treatment, and that blindness occurs 12 years after incident POAG, the present value of the costs of treatment for the cohort would be more than \$900 million or an average of more than \$20 million per year that would be borne primarily by older adults at present, given Medicare policy on prescription medications at this point, and eventually, in part, by the federal government and taxpayers' legislation. Assuming that the blindness brings about an immediate

quality of life loss, the loss would have to be at least 0.23 quality-adjusted life-years for each year of blindness in order to make the incremental cost-effectiveness ratio less than \$100 000 per quality-adjusted life-year. A gain of 0.23 on a health-related quality of life scale ranging from 0 to 1 (where 0 is death and 1 is perfect health) is a substantial gain, especially for older adults who are unlikely to achieve a score of 1 regardless of their vision.

The assumption that a quality of life loss will occur immediately when blindness occurs and that no quality of life loss occurs when taking a chronic medication is overly generous to prevention. Jampel et al¹⁵ have found that medical therapy can alter and potentially diminish one's quality of life. Factors such as compliance, allergy, long lashes, discomfort, and tearing can significantly affect daily life. This would make the necessary gain from the avoidance of blindness in older adults even higher.

However, if only high-risk individuals were considered, the ability to affect a larger proportion of the population sooner would require a smaller gain to make prevention a cost-effective measure. One study showed a decrement in utility associated with binocular blindness of 0.477, but in reality only a fraction of this effect would occur at 12 years after the onset of POAG and many patients will not suffer binocular blindness before they die.¹⁶

The costs of complications associated with the medications—arrhythmias, depression, or bronchoconstriction—include systemic medical testing, more medications to treat these complications, and perhaps even hospitalizations.¹⁷ These costs would increase the necessary gain in health-related quality of life in order to achieve a potentially cost-effective preventive measure.

We still do not know the best time in the course of the glaucomatous process to initiate therapy. Does the rate of perimetric loss diminish if we treat glaucoma early in the disease? We do not know if the disease progresses more rapidly if therapy is begun once reproducible perimetric damage occurs so that earlier intervention assures a better

disease course. Or is the course of the disease unaltered until later in the disease? This may be better answered by the Early Manifest Glaucoma Trial, whose results will be published shortly.

It may be that medical therapy can prevent or retard the development of glaucomatous damage, but we must now question whether it is correct to treat these eyes. Ocular hypertension remains an extremely important risk factor for disease but is not itself a disease. Instead of recommending treatment for moderate- to high-risk individuals, we suggest that these individuals be seen annually or semiannually, have adequate high-quality baseline documentation of their optic nerves and visual fields, and that both the patient and the physician have an obligation not to miss follow-up evaluations. As this study has also shown us, we should remember that one visual field with earliest detectable changes is not proof of the development of glaucoma.¹⁸ At least 2 visual fields are necessary to document visual-field loss.¹⁹ Before expensive and quality of life-limiting therapy is begun, we must ensure that a disease actually exists and that a glaucomatous process has begun.

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The authors have no relevant financial interest in this article.

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We Should Treat Fewer Patients With Elevated Intraocular Pressure Now That We Know the Results of the Ocular Hypertension Treatment Study

THE OCULAR HYPERTENSION Treatment Study (OHTS), a landmark trial in glaucoma therapy, has definitively answered the question "Does lowering intraocular pressure (IOP) in persons with elevated IOP but no glaucoma damage reduce the incidence of glaucoma?", confirming what most ophthalmologists knew—that treatment works.

However, even the most ardent supporters of treatment to lower IOP would concede that the results of the study do not suggest that all persons with ocular hypertension should be treated.^{1,2} After all, only 9.5% of the subjects who were observed without therapy developed glaucoma during a mean follow-up period of 6 years. As the authors of the study themselves conclude in their article, "The results of the OHTS do not imply that all individuals with elevated IOP should be treated with ocular hypotensive medication."^{3(p708)} Others may look at the OHTS results with a "number needed to treat" perspective⁴ and

conclude that to prevent glaucoma damage in 1 person with ocular hypertension, 20 persons need to be treated.

If the OHTS investigators had supplied us with this information only, we would be hard pressed to know how to apply it to our clinical practice. Fortunately, they have provided us with an analysis of risk factors for the development of glaucoma that allows us to think more critically about whom we decide to treat.⁵ Of greatest importance is the role of central corneal thickness (CCT) as a risk factor for the development of glaucoma. The investigators of the OHTS were able to stratify risk based on a combination of IOP and CCT. They demonstrate that for untreated subjects in the OHTS with IOP ranging from 24 to 32 mm Hg, the risk of incident damage varied 18-fold. Subjects with an IOP of 23.75 mm Hg or lower and a CCT of 588 μ m or less had a 2% incidence, whereas subjects with an IOP of higher than 25.75 mm Hg and a CCT of 555 μ m or less had an incidence of 36%.

The relatively low risk of damage shown in the OHTS for eyes with relatively low elevated IOP and the influence of CCT on the risk profile should lead to the treatment of fewer patients with elevated IOP. Before the OHTS, data on the rate of conversion to glaucoma in patients with ocular hypertension were limited. Without firm data, many practitioners probably felt that it was better to treat all subjects with elevated IOP because the risk of developing glaucoma damage might be very high (even in the absence of a proven treatment effect). With the OHTS data, we can now find good reason not to treat many individuals with elevated IOP measurements only.

Suppose that one's practice pattern was to treat select individuals with an IOP lower than 21 mm Hg but treat all patients with an IOP of 21 mm Hg or higher (it would not surprise me if this were a common practice among ophthalmologists). Based on the OHTS, we now know that some of these individuals with an IOP of 21 mm Hg or higher have thick corneas, suggesting that their

to submitting the manuscript. If we agree that expedited publication has merit, we will work with the authors to establish a timetable for the submission, review, and, if accepted, publication of the manuscript. We will identify reviewers who will agree to a 1-week turnaround time for the review. We will be willing to review a near-final version of the manuscript with the understanding that minor updates to the data may be made in conjunction with responses to reviewer comments. We recognize that in multicenter trials, changes to a manuscript can be time-consuming owing to the number of individuals involved, possibly including a writing committee, a large number of investigators, a data and safety monitoring committee, and the funding entity. For manuscripts that are designated for expedited review, to facilitate a rapid revision of the manuscript when we believe a revision is warranted, we will indicate in a cover letter accompanying the critiques which reviewer comments we believe are most important to address. Once the manuscript is accepted, the time to publication can be as short as 8 weeks. Thus, if we are contacted prior to submission so that reviewers can be contacted for expedited review, the time from submission to publication can be as short as 10 weeks.

For major randomized trial reports, we recognize that publication of the manuscript is just one part of the process of disseminating the results. We will work with the authors to coordinate press releases timed to publication and presentation of the results. In general, we have a strong preference that clinical trial results of public health importance be published prior to public dissemination.

We believe that this best serves the ophthalmologic community by providing the opportunity to fully evaluate the trial methods and results rather than giving a snippet of the methods and results in a presentation or a press release. However, we recognize that there are exceptions, and there may be a trial result that is of such importance for patient care that a delay of several months in disseminating the results is undesirable.

Finally, an additional benefit to publication in the ARCHIVES is the potential for dissemination of the results in other AMA journals. When a clinical trial manuscript is submitted to the ARCHIVES, it will also be considered for publication in JAMA. If accepted for publication in the ARCHIVES, the abstract will be considered for publication in JAMA.

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Correction

Error in the References. In the article titled "The Ocular Hypertension Treatment Study: Intraocular Pressure Lowering Prevents the Development of Glaucoma, but Does That Mean We Should Treat Before the Onset of Disease?" published in the March issue of the ARCHIVES (2004;122:376-378), reference 9 should have read: Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. *Invest Ophthalmol Vis Sci*. 1997;38:83-91.