Comparison of Glaucomatous Progression Between Untreated Patients With Normal-Tension Glaucoma and Patients With Therapeutically Reduced Intraocular Pressures

COLLABORATIVE NORMAL-TENSION GLAUCOMA STUDY GROUP*

• PURPOSE: To determine if intraocular pressure plays a part in the pathogenic process of normal-tension glaucoma.

• METHODS: One eye of each eligible subject was randomized either to be untreated as a control or to have intraocular pressure lowered by 30% from baseline. Eyes were randomized if they met criteria for diagnosis of normal-tension glaucoma and showed documented progression or high-risk field defects that threatened fixation or the appearance of a new disk hemorrhage. The clinical course (visual field and optic disk) of the group with lowered intraocular pressure was compared with the clinical course when intraocular pressure remained at its spontaneous untreated level.

• RESULTS: One hundred-forty eyes of 140 patients were used in this study. Sixty-one were in the treatment group, and 79 were untreated controls. Twenty-eight (35%) of the control eyes and 7 (12%) of the treated eyes reached end points (specifically defined criteria of glaucomatous optic disk progression or visual field loss). An overall survival analysis showed a statistically significant difference between the two groups ($P < .0001$). The mean survival time ±SD of the treated group was 2,688 ± 123 days and for the control group, 1,695 ± 143 days. Of 34 cataracts developed during the study, 11 (14%) occurred in the control group and 23 (38%) in the treated group ($P = .0075$), with the highest incidence in those whose treatment included filtration surgery.

• CONCLUSIONS: Intraocular pressure is part of the pathogenic process in normal-tension glaucoma. Therapy that is effective in lowering intraocular pressure and free of adverse effects would be expected to be beneficial in patients who are at risk of disease progression. (Am J Ophthalmol 1998;126:487–497. © 1998 by Elsevier Science Inc. All rights reserved.)

Accepted for publication May 26, 1998.

The study was generously funded by the Glaucoma Research Foundation, with special grants from the Oxnard Foundation and the Edward J. Daly Foundation, San Francisco, California.

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WHEN TREATING PATIENTS WITH NORMAL-tension glaucoma, ophthalmologists must often decide if intraocular pressure should be lowered, as it is in patients with glaucoma who have elevated intraocular pressure. The assertion that asymmetric normal-tension glaucoma is often associated with asymmetric intraocular pressure suggests that the level of intraocular pressure, even when statistically normal, is still a contributing factor to optic nerve damage; this presents a rationale for lowering intraocular pressure in patients with normal-tension glaucoma.[1–3] Among patients with normal tension glaucoma, there is an

See also pp. 578–581.

0002-9394/98/$19.00
PII S0002-9394(98)00223-2

inverse correlation between intraocular pressure and neural rim area.[4] Yet, it appears that risk factors other than intraocular pressure must be present[5–15] and when identified might be ameliorated by appropriate therapeutic intervention.

To ascertain the influence of intraocular pressure level on the course of normal-tension glaucoma, this prospective multicenter study compared an untreated group of normal-tension glaucoma patients with patients in whom intraocular pressure was lowered by 30%. It was necessary to include an untreated control group in order to validate the influence of intraocular pressure on the course of the disease and the effectiveness, if any, of treatment on the progression of the disease. This includes ensuring that the aggressive measures needed to lower intraocular pressure substantially were not detrimental to these patients. It was also the aim to learn more about the untreated natural history of the disease.

This paper deals with the analysis of our data in which the course of eyes in the control group was followed up from the baseline state at the time of randomization, whereas the course of treated eyes was followed up from a new baseline established as soon as the 30% intraocular pressure reduction was stable, an average of 219 ± 158 days after randomization. Comparison of the two groups will help establish whether patients with lowered intraocular pressure do better when followed up over time, once intraocular pressure is lowered by whatever means. In a companion paper,[16] we discuss a traditional clinical trial "intent-to-treat" analysis in which the inability to achieve 30% lowering of intraocular pressure, progression that might occur before intraocular pressure lowering is achieved, compliance issues, and the visual complications of achieving a lowered intraocular pressure are included, with both groups followed up from a baseline measured at the time of randomization.

PATIENTS AND METHODS

TWO HUNDRED AND THIRTY PATIENTS FROM 24 CENTERS were enrolled in the study. The study was approved by the ethics committees of all the participating centers, and all patients signed written consent forms after the study was explained. A monitoring and safety committee regularly inspected the data for statistically significant outcomes and possible adverse events.

To be included, patients had to have unilateral or bilateral normal-tension glaucoma with optic disk abnormalities and visual field defects judged by the collaborating ophthalmologists to be characteristic of glaucoma and to have had no recorded intraocular pressure over 24 mm Hg in either eye. Patients had to be older than 20 years and younger than 90 years. After a 4-week wash out of any existing medication, all patients had 10 baseline intraocular pressure readings taken, of which six were taken between 8:00 AM and 6:00 PM on one day and the other four readings on other days. The median of the 10 readings was required to be 20 mm Hg or less, with no reading above 24 mm Hg and no more than one reading of 23 or 24 mm Hg. All patients were required to have three good baseline visual fields, performed within 1 month, with the Octopus program 32 or the Humphrey Visual Field Analyzer 30-2 (Humphrey-Zeiss, San Francisco, California) full threshold program, including the point of fixation. A pupil diameter of 2.5 mm or greater was required. A reliable field had to meet three criteria: false positive rate 15% or less, false negative rate 30% or less, and fixation loss less than 15%. These rather strict reliability criteria were chosen in the very early days of computerized perimetry, before the currently less stringent reliability criteria became common guidelines. If the fixation loss was less than 10%, then a false negative rate between 30% and 50% was deemed acceptable. No more than five attempts to achieve the three reliable fields was allowed. This was done to exclude patients with inconsistent visual field examinations because visual field examinations are the primary means to recognize progression and to judge outcome. A minimal visual field defect consisted of a cluster of 3 adjacent points depressed by at least 5 dB from normal age values, with one of these points depressed by at least 10 dB from normal values for age. At least 3 points of such a cluster, including the 10-dB depressed point, were required to be on one side of the horizontal meridian. There had to be other points elsewhere that were at least 10 dB higher than the densest point in the scotoma.

Patients taking systemic beta-blockers or clonidine and in whom these drugs could not be discontinued were excluded, as were patients who were unable to perform reliable fields or who had a nonglaucomatous condition that might later affect the visual field. Also excluded were eyes with previous laser treatment, previous ocular surgery (except strabismus surgery), or cyclodestructive procedures; eyes with field defects attributable to nonglaucomatous conditions (for example, traumatic choroidal rupture or branch vascular occlusions), narrow anterior chamber angles judged to be occludable and corneal abnormalities; eyes with best-corrected visual acuity less than 20/30; or eyes with visual fields too damaged to detect further progression reliably (at least 9 adjacent points with measurable thresholds to a size 3 stimulus had to be present).

Baseline information on demographics and medical history was recorded, and a complete eye examination was performed. Examination for compressive lesions or carotid artery disease, especially in unilateral cases, was undertaken according to the clinical judgment of the collaborating clinician. Stereo photographs (2X) and a macular test or 10-2 program on the Humphrey perimeter were obtained.

One eye of each patient was entered into the study for randomization to the untreated control arm or to the 30% intraocular pressure reduced arm of the study. When entered into the study, randomization was conducted immediately if the selected eye had a visual field defect that threatened fixation or the reading committee was provided with past visual field examinations that it felt documented recent progression. Otherwise, follow-up examinations were scheduled at a minimal frequency of every 3 months for the first year and every 6 months thereafter, until either a visual field change was documented, a change in the optic nerve head appearance was confirmed, or a disk hemorrhage was noted. It should be noted that although disk hemorrhages indicate an active disease process at the optic nerve and are often followed by disk and visual field changes, and hence reason for randomization, the occurrence of a hemorrhage did not constitute an end point. During these visits, at least the best-corrected visual acuity, the visual field, and the appearance of the optic disk were documented. Photographs of the optic disk were obtained annually, whenever a disk hemorrhage was observed, or whenever a change in the cupping was suspected by the patient's clinician. The photographs were evaluated by the reading committee only if the attending ophthalmologist suspected a change had occurred that was not reflected in the visual field, which is the primary means of judging the course of the disease.

In patients with unilateral normal-tension glaucoma, the eligible eye was followed up until progression occurred and was then randomized, unless fixation was threatened from the outset in which case randomization was performed after baselines were established. In patients with bilateral disease in whom fixation was threatened in only one eye, the nonthreatened eye was selected as the study eye and randomized when it met the criteria for randomization. If fixation was threatened in both eyes, the less affected eye was randomized at the outset. The less affected eye was determined initially if there was a difference of 3 dB or more between the eyes in the mean of the three baseline mean defects (MDs). If the MD difference was smaller than 3 dB, the eye with the lower median intraocular pressure (a difference of 3 mm Hg or greater) was selected. If the eyes were within these limits of MD and intraocular pressure, then the eye to be included in the study was randomly selected. The eye not selected for the study was treated at the discretion of the attending ophthalmologist but without medications that could influence the study eye. In patients in whom both eyes were eligible and neither threatened fixation, both were followed up untreated in the study. The first eye to progress (as defined by the protocol) was randomized. If both eyes showed progression simultaneously, the less affected eye, using the criteria outlined, was randomized.

When the study eye had been selected and met the criteria, randomization was carried out within the participating centers according to Zelen's block randomization scheme[17] to assure approximately equal numbers of patients in each arm of the study in each center. Block sizes were varied to eliminate bias attributable to knowledge of the block size. The study was monitored on an ongoing basis for early demonstrable statistical evidence of treatment effi-

cacy or lack thereof, using the sequential double triangular test and the PEST 3 program.[18]

Patients were randomly assigned to one of two management strategies: to be followed up untreated, or to have intraocular pressure reduced 30% from the mean of the last three prerandomization pressure readings by medical or surgical intervention. Subsequently, treatment was augmented as required to maintain the 30% reduction in intraocular pressure. In patients undergoing filtration surgery, a 20% intraocular pressure reduction was accepted without requiring the patient to undergo a second procedure, and no more than three surgical procedures were called for by the protocol in an effort to achieve the intraocular pressure goal. Because the study was designed to examine the effects of intraocular pressure reduction, neither eye could be treated with beta-adrenergic blockers or adrenergic agonists because of their potential cardiovascular and crossover effects that could confound the data. Systemic carbonic anhydrase inhibitors could be used only when the study eye had been randomized to the intraocular pressure lowering group. The goal was to achieve the 30% pressure lowering within 6 months, but in fact, it often took longer. All randomly assigned patients were monitored for occurrence of visual field progression, change in degree of glaucomatous optic disk damage, or both.

The protocol definition of visual field progression ensured identification of minimal field alterations to minimize any risk to eyes in the untreated control arm of the study. These criteria consisted of a deepening of an existing scotoma, the expansion of an existing scotoma, a new or expanded threat to fixation, or a fresh scotoma in a previously normal part of the visual field. To meet the first two criteria, two adjacent points in a baseline defect needed to have declined 10 dB from their initial average of the three baseline values. The decline must also have been at least three times the short term fluctuation, and furthermore, the threshold sensitivity had to have been worse than any value at that location in any of the three baseline visual fields. A new defect was defined as a cluster of at least 3 points meeting the criteria for a visual field defect occurring in a previously normal part of the field. A new threat to fixation was considered to have occurred when one paracentral point that was normal in all three baseline visual fields became sufficiently abnormal to meet the definition of a threat to fixation, or became included within a defect that constituted a pre-existing threat to fixation, thus expanding its boundary. Any visual field progression had to be verified on two of three fields done within 1 month and verified in two of three fields done 3 months later. On each confirming field, the points showing progression need not have been the very same points, but in the same region, at least 50% of the points had to be the same, and the adjacency requirement remained unchanged.

If the supervising ophthalmologist judged that optic disk changes occurred, photographs were submitted so that the change could be confirmed by the reading committee. Both members of the reading committee (D.R.A., S.M.D.) were independently presented with masked sets of stereo disk photographs. Independently, they had to agree that the degree of glaucomatous damage was different in the two stereo pairs, and both had to identify correctly the baseline photographs.

When an end point was reached by virtue of disk progression or visual field loss (as defined), all therapeutic constraints were also lifted, and the patients were treated according to the individual clinician's judgment. The above end points were used to guide the decision as to when the patient was released from protocol constraints. Modified data collection was, however, continued.

For the purpose of analyzing study outcomes, we developed software to identify an end point in a follow-up visual field relative to the three baseline fields (the three baseline visual fields were at the time of randomization in the untreated observation arm but at the time of intraocular pressure stabilization in the treated group) according to the following four-of-five criteria: a follow-up visual field was said to show progression relative to baseline if it contained 2 or more points that had changed by at least 10 dB, relative to the average baseline values for these points. These 2 progressing points had to be adjacent to each other, both could not be peripheral, not crossing the nasal meridian, and the sensitivity at each deteriorating point had to be less than the minimum of the values of this point in each of the three baseline visual fields. In addition, progression was also deemed to have taken place if

at least 1 of the innermost 4 points showed at least 10-dB deterioration relative to its average value at baseline, with a value that was less than its minimum value in each baseline field. Progression was considered to be confirmed when four of five consecutive follow-up fields showed progression relative to baseline fields, with at least one nonperipheral progressing point (or the one central point) being common to all four fields.

The investigators were asked to identify all patients in the study whose best-corrected visual acuity diminished by 2 lines or more on the Snellen chart and those in whom the foveal thresholds became abnormal. For either of those occurrences, they then had to determine whether this was caused by glaucoma, cataract, macular degeneration, hypotony induced macular edema, other forms of macular edema, other causes, or was undetermined. Further details of the study design have been published.[19]

Kaplan-Meier survival analysis was carried out to compare the survival experience of the treated and untreated groups. Cox regression analysis was used to adjust for covariates (for example, change in intraocular pressure). These analyses were carried out both on the basis of the protocol definition of end point and on the basis of the corresponding four-of-five definition discussed above. After determining the relative equivalence of these two methods in terms of sensitivity and specificity, we used the four-of-five method for subsequent analyses because it presented greater flexibility and speed in carrying out these comparisons.

After analyzing the raw data, we repeated the analysis after taking a number of steps to correct for potential sources of bias in the data when performing the survival analyses. In particular, we compared the log-transformed intervisit time intervals in the two study groups by means of nested analyses of variance for different years of follow-up and overall. To control for the potential bias of false positive calls of end points because of a higher frequency of follow-up visits in one group, we thinned the data in the group with the significantly higher visit frequency by a random mechanism, matching the frequencies, the mean intervisit times, and corresponding variances between the two groups on a year-by-year basis.

TABLE 1. Baseline Characteristics of the Treated and Untreated Control Groups (Means ± SD)

	Control Group (n = 79)	Treated Group (n = 61)	*P*
Age (yrs)	65.5 ± 9.6	66.3 ± 10.3	.63
Sex			.21
Male	30	17	
Female	49	44	
Ethnicity			.26
Asian	9	3	
Black	2	5	
Hispanic	2	1	
White	65	51	
Refraction	−0.66 ± 2.86	−1.09 ± 3.3	.42
Visual acuity	0.89 ± 2.86	0.89 ± 0.15	.86
MD at randomization	−7.54 ± 4.31	−8.38 ± 5.26	.32
IOP at randomization (mm Hg)	16.1 ± 2.3	16.9 ± 2.1	.02

MD = mean defect; IOP = intraocular pressure.

To correct for the potential biasing effect caused by the time lag between randomization and stabilization in the treated group, which led to baselines in the treated group being measured later than in the control group, we defined new baselines for the control group with a delay after randomization that was matched to the corresponding delays in the treated group. The survival experience of the thinned and time-matched data was reanalyzed.

To correct for the possibility that end points may have been identified because of cataracts noted during the study rather than to glaucomatous progression, we carried out a sensitivity analysis by censoring the data from patients in both groups at the time of the cataract diagnosis and reanalyzing the adjusted data for survival.

RESULTS

TWO HUNDRED AND THIRTY EYES WERE ENROLLED IN the study. All 145 eyes of 145 patients meeting the randomization criteria by virtue of showing progression as defined or having a threat to fixation at the time of recruitment were randomized. Five eyes in the treatment group were randomized but withdrew from the study before their intraocular pressure stabilized and therefore provided no information for

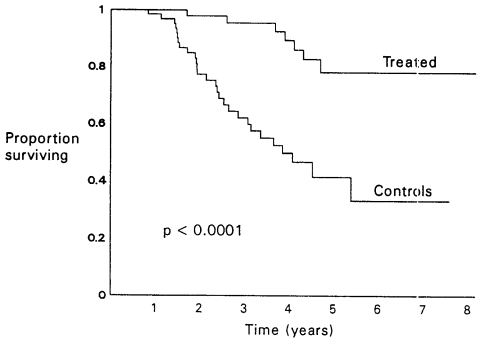

FIGURE 1. Survival curves of untreated control subjects and treated patients from randomization using protocol-defined end points.

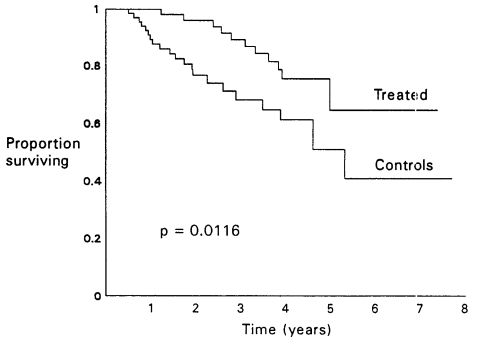

FIGURE 2. Survival curves of untreated control subjects and treated patients from randomization using the "four-of-five" end points.

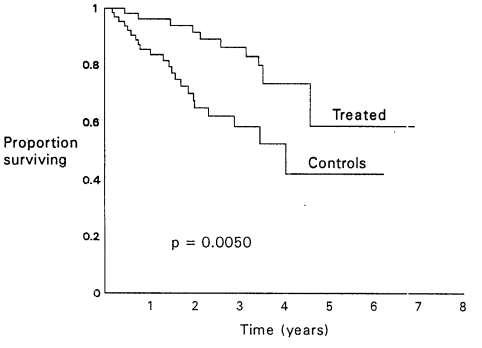

FIGURE 3. Survival curves of untreated control subjects and treated patients from stabilization using the "four-of-five" end points.

this part of the study. They are, however, included in the subsequent intent-to-treat analysis. Of the 140 eyes, 79 (56%), of which 50 (63%) had an initial threat to fixation, were randomized to no treatment. Of the 61 (44%) eyes randomized to treatment, 42 (64%) had an initial threat to fixation. The demographic composition of the two groups is shown in Table 1. The only statistically significant difference between the two groups is intraocular pressure at the time of randomization, which was slightly higher in the treated group (P = .0224).

By the end points outlined in the protocol, 28 (35%) of the 79 untreated control eyes reached end point, three having had only a disk change. In the treated group, seven (12%) of the 61 eyes reached an end point, one having had a change in the disk alone. Using the four-of-five field change progression criteria, 24 (30%) of the 79 untreated control eyes reached an end point, three of which had a disk change alone, whereas 11 (18%) of the 61 treated eyes reached an end point. In the one eye in the treated group, which showed a disk change as the end point, when the protocol criteria for visual field end points were used, visual field end points preceded the disk change when the four-of-five criteria were used.

An overall survival analysis, using the protocol definition of progression, showed a statistically significant favorable effect of lowering intraocular pressure on the visual field and optic disk (P < .0001, Figure 1). There were 35 end points of which 28 occurred in the untreated control group and seven in the treated patients. Mean survival time (± SD) from randomization (based on a statistical estimate derived from patients who did not reach end point and were censored, and on the actual survival time of those who had reached an end point) for the treated group was 2,688 ± 123 days and for the control subjects, 1,695 ± 143 days. The corresponding four-of-five analysis was somewhat more conservative (P = .01, Figure 2), with the mean survival time in the treated group of 2,255 ± 118 days and mean survival time in the control group of 1,837 ± 168 days. There were 32 end points of which 21 were in the untreated control group and 11 in the treated patients.

Analysis of variance showed that the control group had more frequent follow-up visits annually than the treated group (P = .002) in each follow-up year. The control group had a mean time interval between visits

TABLE 2. Comparison of Follow-up Results Between the Treated and Untreated Control Groups*

	Control Group (n = 79)	Treated Group (n = 61)	*P* value
MD at stabilization	−7.54 ± 4.31	−9.42 ± 4.82	.02
IOP during follow-up (mm Hg)	16.0 ± 2.1	10.6 ± 2.7	<.0001
MD during follow-up	−8.08 ± 4.28	−9.62 ± 4.53	.05
MD slope during follow-up (dB per year)	−0.4018 ± 3.65	−0.4992 ± 1.97	.85

MD = mean defect; IOP = intraocular pressure.
*Values are mean ± SD unless otherwise indicated.

± SD of 3.2 ± 0.1 months and 3.9 ± 0.1 months for the treated patients. Statistical thinning, as described in Methods section, equalized the frequencies (P = .4). The thinned control data were then compared by survival analysis to the treated group. Again the treated group did better (P = .021).

We repeated the survival analysis on the thinned control data, having further selected time-lagged baselines for the control group to match the delays in the treated group between randomization and stabilization. The thinned, time-matched survival analysis again showed a significant improvement with treatment (P = .005, Figure 3), with mean survival time ± SD (from randomization) of 2,049 ± 129 days in the treated group versus 1,427 ± 139 in the control group. There were 33 end points of which 22 were in the untreated control eyes and 11 in the treated eyes.

To determine whether survival depended on the degree of intraocular pressure reduction within each treatment group, a Cox regression analysis was carried out, with mean overall pressure change relative to baselines as patient-dependent covariate. Neither the absolute nor the percent change in intraocular pressure over the follow-up period showed any significant association with survival within either group. The intraocular pressure values and the MD values over the period of follow-up are presented in Table 2.

Of the 34 cataracts identified during the study, 11 (14%) occurred in the control group and 23 (38%) in the treated group (P = .0011). Of the 23 cataracts in the treated group, 16 (26%) had been treated surgically and seven (11%) medically (P = .059). The rate of development of cataracts in the untreated control subjects was significantly lower than in the surgically treated subgroup (P = .0001) but not statistically different from the rate in the medically treated subgroup (P = .18).

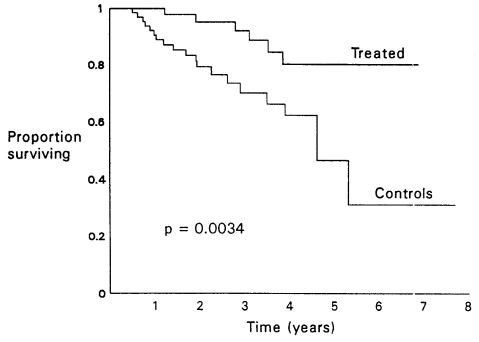

FIGURE 4. Survival curves of untreated control subjects and treated patients from randomization using the "four-of-five" end points after eyes that developed a cataract were censored.

The mean ± SD time to cataract (from randomization) was 1,443 ± 785 days in the control group; in the treated group, it was 1,200 ± 694 days (P = .31). The mean time in the medically treated eyes was 1,266 ± 648 days and in the surgically treated eyes, 1,168 ± 732 (P = .75). In the treated group, the mean time to cataract from the poststabilization baseline was 822 ± 687.2 days. Survival analysis with the cataracts taken as censored observations at the time of diagnosis showed, again, a favorable treatment effect (P = .0034, Figure 4), with mean control survival time ± SD of 1,783 ± 185 days and mean treatment survival time of 2,242 ± 108 days. There were 25 end points of which 19 were in the untreated control eyes and six in the treated eyes.

DISCUSSION

SHORTLY AFTER THE INTRODUCTION OF THE OPHthalmoscope, when the cupping of the optic nerve head was recognized as a feature of glaucomatous optic neuropathy, von Graefe[20] recognized the existence of optic nerve head abnormality, with disturbances of vision, with digitally estimated normal intraocular pressure. His colleagues so severely criticized this concept that he later recanted but con-

tinued to stress that different optic nerves might have different susceptibilities to intraocular pressure. Schnabel[21] drew attention to the fact that most ophthalmologists were aware of these cases, in spite of von Greafe's denial that they existed, and that an explanation should be found to account for all of the glaucoma patients rather than to deny the existence of those whose pressures are not elevated. The introduction of the impression tonometer by Schiotz confirmed the existence of the entity, but it was considered to be very rare.

The explanation for these unusual cases was usually sought in the inadequacy of periodic pressure recordings to find the abnormally elevated intraocular pressure. It was also suggested that some patients might be damaged by high pressures, but with aging, decreased aqueous secretion might produce a decline in intraocular pressure so that the patients really show a "burnt out" phase of the disease. The concept of damage to the optic nerve from sclerotic internal carotid arteries was also entertained. Population studies in the United Kingdom,[22–24] Sweden,[25,26] the United States,[27–31] and Japan[32–34] have drawn attention to the fact that normal-tension glaucoma is by no means a rare event. The subject of glaucoma with normal intraocular pressure was extensively reviewed by Sjogren,[35] who described cerebral atrophy in low-tension glaucoma patients, and later by Levene.[36]

Patients with normal-tension glaucoma present both conceptual and practical problems of management. It is comparatively easy to reduce elevated intraocular pressure, but it is much more difficult to achieve a substantial reduction of intraocular pressure that is already in the normal range. It has also become evident that risk factors other than intraocular pressure must play an important part and perhaps have a dominant role in the pathogenesis of this disease. It is even conceivable that in normal-tension glaucoma, these other risk factors can themselves damage the optic nerve without invoking the intraocular pressure. The other risk factors, many of which remain to be elucidated, are more likely to predominate in those glaucoma patients whose intraocular pressures are in the normal range. Faced with a patient whose intraocular pressure is not strikingly lowered by simple methods, the uncertainty of intraocular pressure influence on the course of the disease makes the clinician hesitate to use more aggressive means with potential adverse side effects or complications. For these reasons, it is important to determine whether the level of intraocular pressure contributes to the rate of progression in patients with normal-tension glaucoma.

In the absence of either evidence or consensus about the risks and benefits of treatment, a randomized trial was clearly ethical. The collaborative study was conceived in 1984 to try to answer the question as to whether intraocular pressure plays any part in producing the optic nerve damage and visual field loss in normal tension glaucoma. Although all agreed that the role of intraocular pressure was quite unproved, some ophthalmologists suspected that intraocular pressure lowering was helpful even though others suspected it was not. This presented an ethical dilemma as to how to design such a study to include an untreated control group. To make the study ethically acceptable to the collaborating investigators and their institutions, it was decided to use only one eye per patient. It was also agreed to enroll the patient's better eye, to exclude advanced disease, and to randomize eyes with threats to fixation immediately, rather than to wait for them to show progression. Furthermore, the increment of visual field progression to end point was defined to be exceedingly small so that management of eyes assigned to no treatment or to treatment with some limitation on options could be quickly released from any constraints on the clinical judgment of the treating physician. The small visual field alterations initially chosen to indicate progression and end points later turned out to be nonspecific[37] and were not included in the final analysis. A greater change and additional confirmation was then required for evidence of genuine progression. While making the occurrence of progression more certain, the degree of deterioration that constituted an end point remained very small.[38] It must not be forgotten that the study protocol was designed before any statistical programs for visual field analysis based on normal and glaucomatous individuals were available.

We arbitrarily picked a 30% pressure reduction believing that to achieve this reduction, filtering surgery would be required. This was particularly likely as we excluded all vasoactive topical medication that could affect the optic nerve beneficially or

adversely. Such effects on the optic nerve would have confounded the interpretation and the identification of any effects of the intraocular pressure reduction, which was the aim of the study.

The study design focused on the question of whether the rate of progression of the disease was the same or different in eyes in which the intraocular pressure had been substantially lowered compared with eyes with intraocular pressure unaltered by therapy. Treatment modalities that might even theoretically have effects on the disease process in ways other than by altering intraocular pressure were avoided. The trial did not focus primarily on a particular treatment modality or management style and in this way, intentionally differed from a traditional clinical trial. The fundamental question of whether intraocular pressure is or is not part of the disease process was an important first step that must be more general and of more lasting importance than the question of whether presently available therapy or the intent to treat was effective, which could be affected by such things as compliance and adverse effects, as well as benefits. The clinical question of whether one should attempt to lower intraocular pressure and by how much depends on such things as the severity and prognosis of the individual case, as well as risk factors and adverse effects from therapy chosen. Furthermore, it cannot be answered by a single clinical trial, the results of which may not apply when new modalities of treatment become available.

Our study shows unequivocally that when intraocular pressure is lowered by 30%, the disease subsequently shows a slower rate of visual field progression than in eyes in which no effort was made to lower intraocular pressure. The study group reported previously that this 30% pressure reduction can be obtained and maintained in nearly half the patients with topical drugs, laser trabeculoplasty, or both.[39] The disease is also often either slow or nonprogressive. Of the randomized untreated eyes, 65% showed no progression during follow-up, as defined by our protocol. Most such patients had been followed-up for 5 years or more, but slow progressors might take longer to become apparent. There are others who would never progress whereas others experience episodic failure. It is also true that even after successful intraocular pressure lowering, some cases showed a sufficient additional increment of visual field loss so that end point was reached. Some of these may represent cases in which lowering of intraocular pressure might have slowed but did not halt the disease process. There may be cases in which pathogenic factors damage the optic nerve quite independently of the level of intraocular pressure.[40]

As we looked at the rate of progression after intraocular pressure had been successfully lowered compared with untreated intraocular pressure, the present analysis speaks simply as to whether intraocular pressure is a factor in the disease. We plan separately to report analyses from the viewpoint of a clinical trial (the outcome compared with the prerandomization baselines rather than the rate of progression of the disease after the intraocular pressure was successfully lowered), the intensity of treatment required to achieve consistently the aggressive goal of 30% lowering of the intraocular pressure, and the adverse events that represent the cost of realizing the benefit. A clinically beneficial outcome requires more than the simple demonstration that intraocular pressure is part of the disease, which was the singular purpose of the analysis presented in this paper. Subsequently, we hope to identify some of the risk factors that influenced the course of the disease and to describe the natural history of the untreated disease, which will provide additional information for making clinical management decisions optimal for the individual patient.

It seems clear that intraocular pressure is involved in the so-called "normal-tension glaucoma" patients. This confirms some of the indirect evidence that incriminated intraocular pressure as being involved in the pathogenesis of normal-tension glaucoma.[1,2,4] Therapy that is effective in lowering intraocular pressure and free of adverse effects would be expected to be beneficial in patients who are at risk of progressing. The clinical decisions pertaining to the management of the disease depend also on other considerations to be more fully explored in upcoming manuscripts from the study.

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