The Effectiveness of Intraocular Pressure Reduction in the Treatment of Normal-Tension Glaucoma

COLLABORATIVE NORMAL-TENSION GLAUCOMA STUDY GROUP*

• PURPOSE: In a companion paper, we determined that intraocular pressure is part of the pathogenesis of normal-tension glaucoma by analyzing the effect of a 30% intraocular pressure reduction on the subsequent course of the disease. We report an intent-to-treat analysis of the study data to determine the effectiveness of pressure reduction.

• METHODS: One eligible eye of 145 subjects with normal-tension glaucoma was randomized either to no treatment (control) or to a 30% intraocular pressure reduction from baseline. To be eligible for randomization, the normal-tension glaucoma eyes had to show documented progression of field defects or a new disk hemorrhage or had to have field defects that threatened fixation when first presented for the study. Survival analysis compared time to progression of all randomly assigned patients during the course of follow-up from the initial baseline at randomization. In a separate analysis, data of patients developing cataracts were censored at the time that cataract produced 2 lines of Snellen visual acuity loss.

• RESULTS: Visual field progression occurred at indistinguishable rates in the pressure-lowered (22/66) and the untreated control (31/79) arms of the study (P = .21). In an analysis with data censored when cataract affected visual acuity, visual field progression was significantly more common in the untreated group (21/79) compared with the treated group (8/66). An overall survival analysis showed a survival of 80% in the treated arm and of 60% in the control arm at 3 years, and 80% in the treated arm and 40% in the controls at 5 years. The Kaplan-Meier curves were significantly different (P = .0018). The analyses gave different results because of a higher incidence of cataract in the group that underwent filtration surgery.

• CONCLUSIONS: The favorable effect of intraocular pressure reduction on progression of visual change in normal-tension glaucoma was only found when the impact of cataracts on visual field progression, produced largely by surgery, was removed. Lowering intraocular pressure without producing cataracts is beneficial. Because not all untreated patients progressed, the natural history of normal-tension glaucoma must be considered before embarking on intraocular pressure reduction with therapy apt to exacerbate cataract formation unless normal-tension glaucoma threatens serious visual loss. (Am J Ophthalmol 1998;126:498–505. © 1998 by Elsevier Science Inc. All rights reserved.)

I N OUR COMPANION ARTICLE,[1] THE MULTICENTER Normal-Tension Glaucoma Trial Group showed that reducing intraocular pressure by 30% favor-

ably influenced the course of the disease. This finding substantiated previous reports that suggested

indirectly a role for intraocular pressure, even at statistically normal levels. The incidence of progression in untreated control eyes was greater than in treated eyes when measured from a new baseline obtained after a 30% intraocular pressure reduction had been achieved in the treated group. To use these findings rationally in the management of the disease, one also needs to know how easily and how often such intraocular pressure–lowering can be achieved, as well as the side effects of drugs and complications of surgical intervention required to obtain such a pressure reduction. The traditional randomized clinical trial compares the outcomes of different managements to the baselines obtained at the time of randomization in both groups, whereas the analysis reported in the companion paper[1] compared the two groups from baselines taken after a 30% reduction of intraocular pressure had been obtained. We report the results of an intent-to-treat statistical analysis of the data.

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 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, of which six were taken between 8:00 A.M. and 6:00 P.M. 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 fields, per-

formed within 1 month, with the Octopus program 32 (Interzeag, Schlieren, Switzerland) or the Humphrey Visual Field Analyzer 30-2 (Humphrey-Zeiss, San Francisco, California) full threshold program, including the point of fixation.

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 in the visual field that were at least 10 dB higher than the most depressed 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 a 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).

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 hem-

orrhages 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 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 and 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 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[2] to ensure approximately equal numbers of patients in each arm of the study in each center. Block sizes were varied to eliminate bias caused by knowledge of the block size. The study was monitored on an ongoing basis for early demonstrable statistical evidence of treatment efficacy or lack thereof, using the sequential double triangular test and the PEST 3 program.[3]

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 the 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. The definitions of field progression and disk deterioration are outlined in the companion paper.[1] The final analysis reported here does not include patients in either arm of the study who in the early part of the study reached the nonspecific visual field criteria used and later modified.

When an end point was reached by disk progression or visual field loss (as defined), all therapeutic constraints were also lifted, and 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 at the time of randomization according to the following "four-of-five" criteria: a follow-up visual field was said to show progression relative to base-

line 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, both could not be peripheral, both could not cross 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 one of the innermost 4 points showed at least a 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 attributable to 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 previously published.[4]

The statistical methods used in this analysis are in general analogous to those described in the companion paper.[1] They differ mainly in that the three baseline fields used in the statistical analysis for determining progression in the two groups, in this study, were those taken at the time of randomization, and not, for the treated group, at the later time of intraocular pressure stabilization, as had been done in the companion study. All patients randomly assigned were included in the analysis of the group to which they were randomized. This resulted in sample sizes of 66 treated patients and 79 untreated control subjects. The control subjects were the same as those in the companion study[1]; in the treated group, five additional patients were included who had dropped out fairly early after randomization and did not provide sufficient information for the analyses of the companion paper.

Visual field progression was identified for the present analysis by the "four-of-five" criteria described, as the protocol definition of progression was inappropriate for the present context.

Survival analyses were carried out on the complete data set and again on the thinned data set. In the latter, the frequencies of the visits in the untreated control group were thinned to match those in the treated group, as described in the companion paper.[1] The time-matching technique used in the other study was not required in the present analysis because as all measurements were taken from the point of randomization. The analyses were repeated with the data from patients with cataracts who were censored at the time of the diagnosis of cataract as described.

In the treated group, we calculated the differences between the mean defect (MD) level of the three baseline Humphrey fields and the corresponding mean value of three fields taken at the time of intraocular pressure stabilization. These differences were then compared by an analysis of covariance to corresponding MD differences in the untreated control subjects over matched time intervals from randomization, adjusting for the time intervals and for the initial baseline MD levels as the covariates. This comparison may have been influenced to some degree by a (possibly treatment related) differential effect of MD change caused by development of cataracts in either group. To control for this potential confounding, we adjusted the individual patients' MD values for the corresponding foveal readings by regression analysis. We assumed that changes in foveal sensitivity reflect primarily the effects of cataract formation and are relatively unrelated to changes produced by glaucoma. The changes in the fovea-adjusted net MD values, reflecting more accurately changes attributable to glaucoma in these patients, were again compared between the two groups by means of analysis of covariance, as above. Finally, changes in the foveal values themselves were compared directly over the same time period between the two treatment groups, again using analysis of covariance techniques.

Before the study began, we calculated that if the progression rate was 10% in one arm of the study and 35% in the other, a two-tailed test (5% significance level) would have a power of 90% with 72 subjects and a power of 80% with 57 subjects in
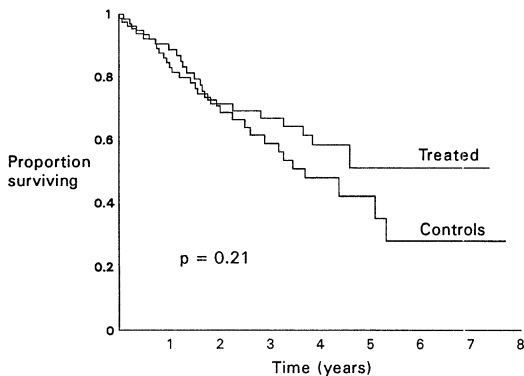
FIGURE 1. Survival curves of end points in untreated control subjects and treated patients from visual field baselines obtained at randomization using 4/5 defined end points fully described in the companion paper.[1]

each arm of the study. Similarly, the difference between 25% in one arm and 50% in the other would be detected with a power of 90% from 92 subjects in each arm and with a power of 80% from 73 subjects in each arm of the study.

RESULTS

OF THE 230 EYES ENROLLED IN THE STUDY, ALL 145 EYES of 145 patients meeting the randomization criteria by virtue of showing progression as defined, a new disk hemorrhage, or having a threat to fixation at the time of recruitment, were randomized. Of these 145 eyes, 79 (55%), of which 50 (63%) had an initial threat to fixation, were randomized to no treatment. Of the 66 (45%) eyes randomized to treatment, 42 (64%) had an initial threat to fixation. It is again emphasized that all eyes randomized were included in this analysis.

A total of 53 end points were observed (31 control subjects and 22 treated patients). Kaplan-Meier survival analysis on the full data, from the time of randomization, showed no significant statistical difference in the survival times before end points are reached between the treated and the control groups ($P = .21$; Figure 1). The estimated mean survival time for control subjects was 1,525 ± 152 days and for the treated group, 1,796 ± 151 days ± SD. With the sample sizes used, the power for detecting a difference in survival rates as small as

the one observed, with a two-sided significance level of 5%, is 11%. To identify this observed difference as significant at the usual power of 80% would have required 1,033 observations in each of the two arms of the study. Cox regression analyses on the same data set showed that within each patient group, the mean change in intraocular pressure, either in mm Hg or in percent from baseline, had no significant effect on survival (P values ranging from .47 to .62).

Survival analysis on the thinned data gave analogous results. The two survival functions were statistically similar ($P = .19$): mean survival time for the control subjects was 1,659 ± 161 days and for the treated group, 1,899 ± 146 days; and in all, 45 end points were observed (26 control subjects and 19 treated patients).

Cataracts occurred in 11 (14%) of 79 control eyes and in 23 (35%) of 66 eyes in the treated group ($P = .0011$). Of these, 16 (48%) were among 33 surgically treated eyes and seven (25%) were among 28 eyes treated only with medication and laser trabeculoplasty ($P = .059$). 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 ($P = .18$).

We repeated the Kaplan-Meier analyses on the full data set, identifying all cataract events (2 lines of Snellen visual acuity loss attributed on the basis of clinical examination) and censoring the corresponding observations at the time the cataracts were diagnosed. With this adjustment, the survival experience became significantly better for the treated group than the control subjects ($P = .0018$, Figure 2). The survival analysis showed a survival of 80% in the treated arm and of 60% in the control arm at 3 years, and 80% in the treated arm and 40% in the controls at 5 years. The mean survival time for the control subjects was 1,476 ± 155 days and for the treated group, 2,101 ± 122 days. A total of 39 end points were observed (29 control subjects and 10 treated patients). The same analysis on the thinned data again showed significantly better survival for the treated group ($P = .013$); in this case, mean survival time for the control subjects was 1,724 ± 186 days and for the treated group, 2,161 ± 119
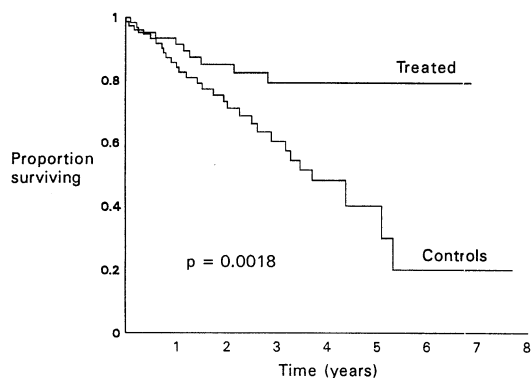
FIGURE 2. Survival curves of end points in untreated control subjects and treated patients from visual field baselines obtained at randomization using 4/5 defined end points with data of eyes developing cataracts censored at the time of the diagnosis of the cataract.

days. Twenty-nine endpoints were observed (21 control subjects and 8 treated patients).

The changes in mean MD from randomization to intraocular pressure stabilization were significantly different between the treated and the untreated control group: after adjustment for baseline and time interval, the mean MD for the treated group fell by 0.98 dB, whereas that of the untreated control subjects increased by 0.08 dB ($P = .001$). The mean MD after adjustment for foveal values showed no significant change between the two groups ($P = .65$). The mean foveal changes between the two groups were significant ($P = .007$); adjusted mean fall in the treated group was 1.07 dB and in control subjects, 0.27 dB.

DISCUSSION

WE HAVE DEMONSTRATED, IN THE COMPANION PAPER, that a 30% reduction of intraocular pressure favorably influences the subsequent progression of disease in normal-tension glaucoma patients compared with untreated normal-tension glaucoma controls.[1] Unlike the effective intraocular pressure lowering achieved analysis, in the companion paper, our present overall "intent-to-treat" survival analysis initially showed no significant difference between the visual field survival experiences of the treated and the untreated control groups. This apparent discrepancy in the results of the two analyses is primarily attributed to the fact that the baseline visual field threshold values of the treated group were higher at the time of randomization (the baseline used in the present analysis) than the baseline values at the time of pressure stabilization used in the analysis reported in the companion paper.[1]

The decline in the levels of these baselines for the treated group from randomization to stabilization was demonstrated above by the highly significant fall in the mean MD values for this group relative to the untreated control subject over the corresponding time interval. Progression is more readily observed during the follow-up period, when a higher baseline is used as a reference. Thus, the number of end points in the treated group was 22 in the present overall analysis from randomization, as compared with only 11 in the corresponding four-of-five overall analysis from the time of intraocular pressure stabilization reported in the companion paper.[1]

It was also shown above, however, that the significant differential decline in the MD values from randomization to stabilization between the two groups disappeared after adjustment of the MD levels for the corresponding foveal sensitivities and that foveal values alone fully accounted for the degree and the significance of the apparent changes in the MD levels observed. To the extent that significant changes in foveal sensitivities represent primarily the effects of the development of cataract and are not likely to be caused by glaucoma, we can conclude that the apparent changes in MD, and thus the corresponding changes in the baseline visual fields, reflected the differences in rates of cataract development in the two groups. This was borne out by the data: the rate of cataract formation in the treated group was 35% and in the untreated control subjects only 14% ($P = .0011$).

The above conclusions were confirmed when the survival analysis was repeated with the data from cataract patients in both groups censored at the time of the diagnosis of their cataracts. The cataract-adjusted survival experience of the treated group was significantly better than that of the untreated controls ($P = .0018$), in agreement with the findings in the analysis in the companion paper.[1]

The difficulties of interpreting glaucomatous progression in the presence of changing lens opacities have been clinically recognized since quantitative perimetry was introduced in the 1920s. The effects of cataracts on automated visual fields of normal and glaucomatous eyes have been systematically studied.[5–10] Cataracts produce mixtures of blur, scatter, and glare. In the present study, cataracts were diagnosed at the time there was a 2 Snellen line loss of visual acuity explained by the presence of clinically observed lens abnormalities and in the absence of other contributing causes. This definition of cataracts might overemphasize lens opacities that produce blur. Light scatter may affect perimetric thresholds more than it affects visual acuity. The analyses in which we corrected the mean deviation of visual field thresholds by the foveal thresholds supported the conclusions reached when we censored observations at the time visual acuity was blurred by cataract. It is likely that most cataracts produced both blur and scatter, so analyses that highlight one or the other yield similar results.

Achieving a 30% intraocular pressure reduction required either topical medication, laser trabeculoplasty, or fistulizing surgery. All of these interventions carry some potential risks. The present analysis demonstrates that when the comparison of the untreated control subjects with the treated patients is made from the time of their randomization, as opposed to the time of the stabilization of the reduced intraocular pressure, the intervention is beneficial to those whose intraocular pressures were lowered if the visual effects of cataracts are excluded from consideration. When not excluded, the higher incidence of cataracts in the treated group masks the benefit of intraocular pressure reduction on the progression of visual field defects. This suggests that if intraocular pressure is reduced with treatments that do not also produce adverse visual effects, patients may enjoy visual field benefits from lowering intraocular pressure. Drugs are now available that were not available for use in this study. The present multicenter trial excluded the use of topical vasoactive drugs, such as the beta-blockers and alpha agonists, and was carried out before the introduction of topical carbonic anhydrase inhibitors and prostaglandins, which would have reduced the number of surgical interventions that were

particularly cataractogenic. Our results, therefore, overestimated the risk/benefit ratio that might occur in current ophthalmologic practice. The successes of modern cataract surgery will also have to be taken into account when deciding whether the risks of cataract and its surgery may be preferable to the loss of further visual field in individual patients with normal-tension glaucoma.[11]

The current trial also shows that many patients with normal-tension glaucoma showed no progression, as we defined it, in the untreated arm of the study. Additionally, a number of enrolled patients showed no progression while not being treated and were therefore never randomly assigned. This is particularly important, as assertive measures that may have adverse effects are often needed to lower the intraocular pressure successfully. Those patients destined to be nonprogressive or only slowly progressive would derive no benefit from treatment but would have been exposed to the risks. To guide our treatment of patients with normal-tension glaucoma, it would therefore be helpful to find those clinical features that may enable us to distinguish the potential progressors from those whose disease is currently stable. The natural history of the untreated disease and the attempts to find predictive risk factors will be the subject of further analyses of the data collected in this study.

It should also be noted that although fewer patients progressed in the treated group, there were nevertheless some who continued to progress after a 30% intraocular pressure reduction. Perhaps, in them, greater intraocular pressure reduction might have been beneficial, but our study interestingly showed no relation between outcome and the pressure levels during the period of observation. It is also conceivable that in patients with normal-tension glaucoma, and possibly even in some patients with glaucoma, there are pathogenic factors that can by themselves damage the optic nerve no matter what the intraocular pressure is[12] or make the nerve more susceptible to intraocular pressure. If so, it would be helpful to identify those in whom the rate of damage will not be affected by lowering the intraocular pressure.

We hope by further analysis of data from this study to find some identifying features of such population subsets, predictive risk factors, or per-

haps clues to risk factors that may be amenable to therapeutic modification.

REFERENCES

1. The Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 1998;126:487–497.
2. Zelen M. The randomization and stratification of patients to clinical trials. J Chronic Dis 1974;27:365–375.
3. Whitehead J. PEST Version 3: statistical software for the planning and evaluation of sequential trials. Reading, U.K.: University of Reading, 1994.
4. Anderson DR. Normal Tension Glaucoma Study. In: Kertes P, Conway MD, editors. Clinical trials in ophthalmology: a sumary and practice guide. Baltimore: Williams & Wilkins, 1998:335–348.
5. Heuer DK, Anderson DR, Feuer WJ, Gressel MG. The influence of refraction accuracy on automated perimetric threshold measurements. Ophthalmology 1987;94:1550–1553.
6. Heuer DK, Anderson DR, Feuer WJ, Gressel MG. The influence of decreased retinal sensitivity on automatic perimetric threshold. Am J Ophthalmol 1989;108:643–650.
7. Lam BL, Alward WLM, Kolder HE. Effect of cataract on automated perimetry. Ophthalmology 1991;98:1066–1070.
8. Budenz, DL, Feuer, WJ, Anderson, DR. The effect of simulated cataract on the glaucomatous visual field. Ophthalmology 1993;100:511–517.
9. Stewart WC, Rogers GM, Crinkley CMC, Carlson AN. Effect of cataract extraction on automated fields in chronic open-angle glaucoma. Arch Ophthalmol 1995;113:875–879.
10. Smith SD, Katz J, Quigley H. Effect of cataract extraction on the results of automated perimetry in glaucoma. Arch Ophthalmol 1997;115:1515–1519.
11. Chen P, Budenz DL. Effect of cataract extraction on the glaucomatous visual field. Am J Ophthalmol 1998;125:325–333.
12. Schulzer M, Drance SM, Carter CJ, Brooks DE, Douglas GR, Lau W: Biostatistical evidence for two distinct chronic open angle glaucoma populations. Br J Ophthalmol 1990;74:196–200.

Authors Interactive®

We encourage questions and comments regarding this article via the Internet on Authors Interactive® at http://www.ajo.com/ Questions, comments, and author responses are posted.