Relative Risk of Progressive Glaucomatous Visual Field Loss in Patients Enrolled and Not Enrolled in a Prospective Longitudinal Study

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Objective: To establish the relative risk of progressive visual field loss in a sample of glaucomatous eyes enrolled in a prospective longitudinal study vs a matched sample of eyes not enrolled in a study.

Methods: The first visual field records of 66 glaucomatous eyes enrolled in a prospective longitudinal study (mean follow-up time, 3.4 years; mean number of visual field tests, 8.3) were matched to 66 eyes from patients not enrolled in a study (mean follow-up time, 3 years; mean number of visual field tests, 3.7). Eyes were matched on the basis of (1) time of enrollment, (2) length of follow-up, and (3) the extent and spatial pattern of visual field loss. Lin-

ear regression of global visual field indexes was used to measure change and the relative risk of progression was calculated for a series of progression criteria sample.

Results: The relative risk of progressive visual field loss was on average 368% (range, 209%-673%) higher in the eyes not enrolled in a prospective longitudinal study.

Conclusion: Selection bias may reduce the risk of progressive visual field loss in patients enrolled in longitudinal studies.

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THERE HAVE BEEN A NUMBER of prospective longitudinal studies involving patients with glaucoma that have reported on the proportion of eyes showing progressive visual field loss.[1-12] The majority report incidence rates of between 2.5% and 7.5% per year in treated eyes, although this figure is sensitive to a number of factors, including the definition of progression.[4] This relatively low incidence rate has led some researchers to suggest that there may be some biases in prospective longitudinal studies that act to reduce the proportion of patients with progressive loss.

The reported incidence rate of progression in retrospective studies is often larger than that of prospective studies.[13-15] Again, this suggests that the recruitment into prospective longitudinal studies might in some way be biased toward those patients less likely to show progression or in some way create an atmosphere where progression becomes less likely. To our knowledge, the existence of a selection bias has not been systematically investigated or quantified.

This article compares a sample of eyes from patients enrolled in a prospective longitudinal glaucoma study with a matched

sample of eyes from patients not enrolled in a study, to quantify the extent of any selection bias. Eyes in both samples were treated by the same health care professionals.

METHODS

Data for this study were retrospectively collected from 66 eyes of 66 patients enrolled in a prospective longitudinal study investigating the role of optic nerve head and nerve fiber layer imaging in the management of glaucoma[16] and from a matched sample of patients attending the outpatient department of Manchester Royal Eye Hospital (MREH). Ethical approval was obtained from the Central Manchester Research Ethics Committee and the study followed the principles of the Declaration of Helsinki.

Longitudinal regression analyses of 2 global indexes were used to measure progression. The first index, mean defect, gives a measure of the depth of loss. This index was generated by the Peridata software package (Peridata Software GmbH, Hürth, Germany) and is slightly different from the index mean deviation generated by the Humphrey Visual Field Analyzer (Carl Zeiss Meditec Inc, Dublin, Calif). We chose to use the Peridata mean defect because (1) both mean defect and mean deviation give good measures of overall sensitivity loss[17] and (2) the Humphrey Visual Field Analyzer does

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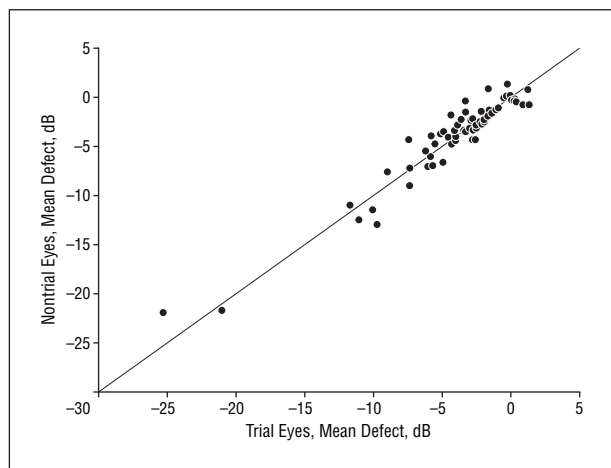
Figure 1. This figure shows how well the study eyes were matched to the nonstudy eyes on the basis of mean defect. Data are taken from the first included visual field record of each eye.

Figure 2. This figure shows how well the study eyes were matched to the nonstudy eyes on the basis of pattern standard deviation (PSD). Data are taken from the first included visual field record of each eye.

not export mean deviation values or provide the means to calculate these values from the exported data. The second index, number of test locations with pattern deviation probability less than 0.05, gives a measure of the spatial extent of loss. This index was generated from custom software.[16] All visual field data were collected with the SITA (31%) or full-threshold (69%) programs of the Humphrey Visual Field Analyzer. Both programs give similar threshold values.[18] All patients were required to have prior experience of threshold perimetry at MREH to ensure that the data were less dependent on learning effects.[19] Data on the length of time that patients were aware that they had glaucoma were not collected. Patients were not included or excluded on the basis of reliability indexes because we did not wish to bias the samples in favor of those who give reliable results. The study eyes were initially selected from patients attending the outpatient clinics of MREH (ie, both samples were selected from the same population of National Health Service patients). All eyes had a clinical diagnosis of open-angle glaucoma based on the appearance of the optic nerve head and visual field loss. The longitudinal study sample was selected to give a wide range of functional loss, extending from early defects to advanced loss. Patients in the longitudinal study attended every 6 months for a period of 3.5 years. At each visit, visual field and imaging (Heidelberg Retinal Tomograph [Heidelberg Engineering, Heidelberg, Germany] and Nerve Fiber Analyzer [Laser Diagnostic Technologies Inc, San Diego, Calif]) data were collected.

The matching of the nonstudy eyes to the study eyes involved several stages: (1) they were matched on the basis of both the period of follow-up (within 150 days) and time of follow-up (first record in the same year); (2) they were matched on the basis of the mean defect (±3 dB) and pattern standard deviation (±3 dB) of the first visual field record; and (3) they were matched on the basis of the pattern of visual field loss. Matching on the basis of the pattern of visual field loss was done by 3 health care professionals who viewed the first visual field record of each study eye and the first visual field record of 5 nonstudy eyes, which matched on criteria 1 and 2. The 3 health care professionals were asked to rank the nonstudy eyes according to the closeness of the spatial match to the study eye. A simple scoring system was then used to select the best spatial match. All patients were older than 38 years at the time of the first included visual field record.

All patients, study and nonstudy, were treated by the same health care professionals within the outpatient department of 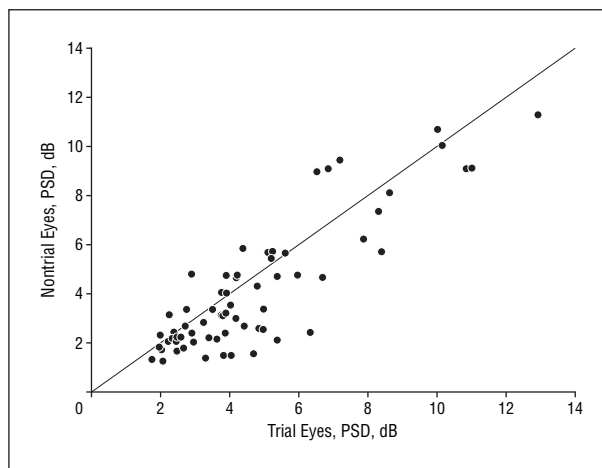MREH. The imaging data from the study patients were not made available to the health care professionals treating the patients, and no patients underwent any ophthalmic surgical procedure during the follow-up period.

RESULTS

Figure 1 and **Figure 2** show that there is good agreement between the study and nonstudy eyes for the indexes mean defect and pattern standard deviation from the first included visual field test record.

Figure 3 and **Figure 4** compare the rates of change for each matched pair of eyes. In Figure 3, far more nonstudy eyes show a more rapid rate of deterioration in the global index mean defect (fall below the diagonal line) than do study eyes. In Figure 4, far more nonstudy eyes show a higher rate of increase in the number of damaged test locations (fall above the diagonal line) than do study eyes.

There are 2 important differences between the data collected from the study and nonstudy eyes. First, the mean number of visual field tests during the follow-up period was larger for patients enrolled in the study than those not enrolled (8.3 vs 3.7). Second, the visual field test results of the study patients were collected by postgraduate researchers working within the Clinical Research Facility rather than visual field technicians working within the more pressured environment of the MREH outpatient department. These 2 differences led to a broader distribution of gradients within the nonstudy sample. When eyes are classified as progressing on the basis of the gradient of the best-fitting line being more negative than a given negative cutoff value, the width of the distribution becomes an important parameter. As the distribution gets wider, for example because of more variability, more eyes will exceed the cutoff value. To overcome this problem, rather than simply look at the number of eyes with gradients lower than the given negative cutoff value, we looked at the ratio of eyes with gradients lower than this value to those with a gradient higher than the reverse gradient (ie, apparent improvers). This ratio will be independent of the distribution width, providing the values are symmetrically distributed (**Table**).
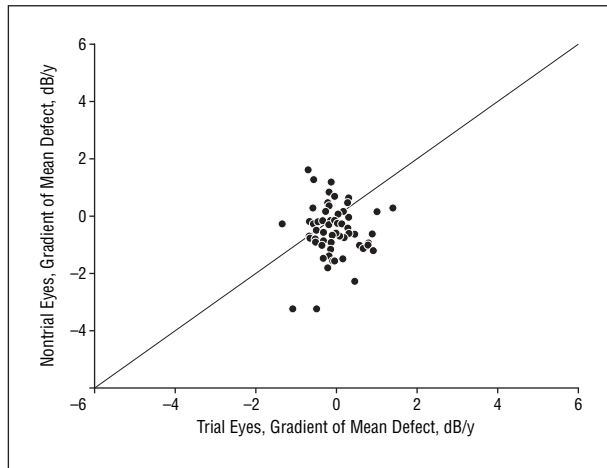
Figure 3. The relationship between the gradient (calculated by linear regression) of the mean defect over time in the study eyes and the matched nonstudy eyes. Points that fall below the diagonal line show more progressive loss in the nonstudy eye compared with the matched study eye.

Figure 4. The relationship between the gradient (calculated by linear regression) of the number of damaged locations (pattern deviation <0.05) over time in the study eyes and the matched nonstudy eyes. Points that fall above the diagonal line show more progressive loss in the nonstudy eye than in the matched study eye.

As can be seen from the Table, this ratio is much greater, for all cutoff values, in the nonstudy eyes. The relative risk of progressive loss in nonstudy vs study eyes is calculated by dividing the ratio of deteriorating to improving nonstudy eyes by the same ratio for study eyes.

The relative risk is dependent on the cutoff gradient. As the cutoff gradient is reduced, an increasing number of eyes will be classified as progressing/deteriorating and any differences between the 2 samples will gradually reduce. Choosing a very steep cutoff will, however, reduce the number of progressing eyes and make the ratio more sensitive to single events. Choosing a cutoff where there is a reasonable number of apparent improvers in both samples ($4 < \times < 9$; 0.60-0.45 dB/y; 1.8-1.3 defects/y) gives average relative risk values of 4.35 for the depth index and 3.27 for the size index.

COMMENT

For some time, a number of researchers have recognized that progressive visual field loss in patients enrolled in prospective longitudinal glaucoma studies is a relatively rare event when compared with data collected in routine clinics. This article presents data that, for the first time, to our knowledge, quantify this effect.

There are 2 likely causes for the differences between the study and nonstudy patients. The first is selection bias. Patients willing to enroll in longitudinal studies are generally more concerned about their condition and are likely to be more attentive, demanding, and compliant with their therapy. Recent reports have shown that compliance/persistence with hypotensive medical therapy is a major problem in glaucoma, with some patients omitting a significant number of doses.[20,21] Chen[22] has shown that those patients who miss lots of visits or refuse surgery (ie, less compliant) tend to do worse, while the results from the Early Manifest Glaucoma Trial[1] have demonstrated that lower intraocular pressure is protective and that noncompliance is likely to result in higher rates of progression.

Table. Ratio of Deteriorating vs Improving Eyes for a Series of Different Cutoff Gradients and the Relative Risk of Progression When Not Involved vs Involved in a Prospective Longitudinal Study

Cutoff Gradient	No. of Deteriorating/ Improving Eyes		Relative Risk*
	Study Eyes	Nonstudy Eyes	
Mean defect, dB/y			
0.7	6/3	27/4	3.38
0.65	5/6	28/5	6.72
0.6	8/7	31/6	4.52
0.55	9/8	33/6	4.89
0.5	13/8	34/6	3.49
0.45	16/8	34/8	2.13
0.4	17/11	35/8	2.83
0.35	19/11	36/8	2.61
Damaged locations, defects/y			
2	4/5	14/4	4.38
1.9	4/6	14/4	5.25
1.8	5/6	16/5	3.84
1.7	5/6	20/5	4.80
1.6	7/6	20/5	3.43
1.5	9/7	20/5	3.11
1.4	11/7	22/6	2.33
1.3	11/7	23/7	2.09
1.2	11/9	24/7	2.81

*The relative risk of progressive loss in nonstudy vs study eyes was calculated by dividing the ratio of deteriorating to improving nonstudy eyes by the same ratio for study eyes.

The second likely cause of the differences in number of eyes showing progressive loss is different management. While patients enrolled in the longitudinal study were clinically treated outside of the study, in the same way and by the same staff as the nonstudy patients, there were a number of differences in treatment that may have led to some bias. Study patients were required to attend every 6 months (ie, more frequently than the nonstudy

patients), and visual field data collected at these visits were made available to the treating health care professional. Treating health care professionals were aware of the patient being involved in this study, and any sudden changes in the patient's condition detected at the study visits would have initiated a prompt review by the treating health care professional. Finally, study patients were, as part of the study, asked if they were experiencing any problems with their medication. Any problems, such as getting repeat prescriptions or insertion of the drops, would have been acted on.

The proportion of progressing eyes within the study sample ranged from 2.6% to 8.5% per year for the selected range of cutoff values. These figures agree with those reported in other trials. Katz et al,[4] when investigating the effect of different definitions of change, reported rates of between 1.75% and 3.65% per year, while Heijl et al[1] reported a rate of 7.5% per year for the treated arm and 10.33% per year for the untreated arm of the Early Manifest Glaucoma Trial. Further study and identification of the differences between the 2 groups could highlight specific risk factors for visual field progression and enable a minimization of visual field loss.

This study has a number of implications for future longitudinal studies. The first is that when estimating sample sizes for studies that seek to investigate changes in the visual field, allowance should be made for the relatively low occurrence of progressive loss in patients who agree to participate. Second, when generalizing from the results of prospective longitudinal studies, account needs to be taken of the likely disparities between study and nonstudy patients.

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