Optic Disc and Visual Field Changes after Trabeculectomy

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PURPOSE. To assess the changes in optic nerve head (ONH) structure and visual field (VF) sensitivity over time in a cohort of patients with glaucoma after trabeculectomy.

METHODS. The MoreFlow Medical Research Council 5-Fluorouracil (5-FU) study was an 80-month prospective randomized controlled trial of per-operative 5-FU versus placebo on the outcomes of primary trabeculectomy. Before surgery, patients had ONH imaging with a retinal tomograph and full-threshold visual field testing. After surgery, ONH imaging was performed annually and VF testing at 4-month intervals. This analysis included only patients with a minimum of 3 years' postoperative ONH and VF data. ONH images were analyzed by linear regression of sector rim area (RA) over time with change defined as a significant slope >1% of baseline RA per year in any sector. VFs were analyzed with point-wise linear regression analysis (PLRA) techniques with the stringent three-omitting criteria used. Eyes were classed as progressing or not based on analysis with either technique. Patients' median IOP level, intervisit IOP fluctuation, and percentage reduction in IOP over the follow-up period were also determined.

RESULTS. Two hundred fifty eyes of 250 patients were suitable for analysis. Of these, 70 (28%) eyes were deemed to show glaucoma progression approximately 5 years after surgery: 20 eyes by ONH alone, 35 by VF alone, and 15 by both methods. Of the 15 shown to be progressing by both ONH and VF analysis, only 7 (5% total cohort) showed congruity in the location of change. Eyes showing changes in both ONH and VF sensitivity had slightly higher median follow-up IOP (median IOP [interquartile range; IQR]) nonprogressors 14.0 mm Hg [11.8–16.0 mm Hg], progressors 15.1 mm Hg [12.7–17.0 mm Hg]; Mann–Whitney U test [MWU]; P = 0.05) and lower degrees of IOP reduction from baseline (percentage IOP reduction [IQR]; nonprogressors −38.4% [−51.8% to −26.4%]; progressors −31.4% [−43.1% to −21.5%]; MWU P = 0.01) compared with eyes showing no progression.

CONCLUSIONS. The study demonstrates that approximately one third of eyes continued to show progression of glaucoma at five years after trabeculectomy, as determined by trend-based analysis of ONH structural changes and VF sensitivity over time. The study suggests that the degree of IOP reduction after trabeculectomy may play an important role in the progression of glaucoma as detected by both functional and structural methods. (Invest Ophthalmol Vis Sci. 2009;50:4693–4699) DOI:10.1167/iovs.08-3115

Glaucoma is a progressive optic neuropathy that results in damage to the retinal ganglion cell axons at the level of the optic nerve head (ONH) with associated changes in visual function. Increased intraocular pressure (IOP) is a major risk factor for the development and progression of the disease1–4; therefore, effective IOP lowering and control remains the primary goal of treatment.

Progression of glaucoma is usually determined by examination of both the visual field (VF) and ONH structure. White-on-white standard automated perimetry (SAP) is an established technique used to measure VF sensitivity. There are several methods available to detect change in VF sensitivity over time using either event-based5–7 or trend-based analyses.8,9 The latter have been shown to have good specificity for detecting change10 and may even be superior to some event-based techniques.9,11 Several imaging devices are available that detect and longitudinally monitor changes in ONH structure. The confocal scanning laser ophthalmoscope (cSLO) was introduced in the early 1990s and was the first device to quantitatively assess the ONH. The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, GmbH, Heidelberg, Germany) is the most established commercially available device and currently offers several strategies to monitor progressive structural ONH changes.12

A popularly held view is that ONH structural changes precede VF loss in glaucoma,13 although in recent times many investigators have found a structure–function dissociation.14,15 and unbiased studies have found that the first signs of conversion or progression may appear in either structural or functional measures.5,16 As a result, most clinicians consider progressive changes in either ONH structure or function (measured by VF sensitivity) as significant, requiring intervention to further lower IOP.

The MoreFlow Medical Research Council 5-Fluorouracil (5-FU) trial was a prospective double-masked randomized controlled trial of the efficacy of per-operative 5-FU on the outcomes of primary trabeculectomy. As part of the follow-up protocol, patients had ONH imaging (HRT) and VF examination with SAP (Humphrey Visual Field Analyzer; HFA; Carl Zeiss Meditec, Inc.) at regular intervals. Although these methods have been used in studies of glaucoma progression to detect changes in patients with ocular hypertension15,17 and in those with established glaucoma,18 data on ONH and VF changes after trabeculectomy are relatively sparse by comparison.

The primary purpose of this study was to examine the longitudinal changes in structure and function, as detected with ONH imaging and white-on-white VF testing in a cohort of

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patients with glaucoma, and to assess the associations of these changes, if any, with IOP level.

METHODS

Subject Selection

The Moreflow Medical Research Council 5-FU Study was a prospective randomized control trial that ran at Moorfields Eye Hospital and the UCL Institute of Ophthalmology from April 1996 to December 2003. Patients who showed progressive glaucomatous disease despite maximally tolerated medical therapy were listed for trabeculectomy and randomized to receiving either per-operative 5-FU or placebo. Three hundred sixty-nine patients were recruited into the original MoreFlow Trial; one eye per patient was enrolled in the study. The study was reviewed and approved by the local research ethics committee and informed consent, according to the tenets of the Declaration of Helsinki, was obtained from each subject before enrolment in the trial. As part of the study protocol, the patients had ONH imaging performed before surgery, at 3-months after surgery, and then at annual intervals for 3 years. At this point, a change in the study protocol was introduced that allowed imaging every 6-months. VF examination was performed before surgery and at 3-month intervals for the first year and at 4-month intervals thereafter (24–2 full-threshold strategy; HFA; Carl Zeiss Meditec, Inc.). Intraocular pressure (IOP) measurement was performed before surgery and at every trial visit (five visits in the first 3 months after surgery, then at 3-month intervals for the first year and at 4-month intervals thereafter).

Optic Nerve Head Analysis

As part of the original 5-FU trial, patients underwent ONH imaging (HRT I or HRT Classic; Heidelberg Engineering, GmbH) with a 15° field of view. For this study, images were analyzed with commercial image-acquisition and -analysis software (Eye Explorer; HeyEx vers. 1.7.0; Heidelberg Engineering GmbH), using the 320-μm reference plane.19 A mean of three HRT images was generated, and a single observer (AK) drew a contour line around the preoperative mean topography (MT), which was subsequently exported to all follow-up MT images in the patient’s series. Misalignment of contour lines was corrected using the manual alignment algorithm of the software.15 Postoperative images were excluded from the analysis if adequate contour line alignment was not possible.

The trend analysis used was a linear regression analysis (LRA) of sector rim area (RA) over time described by Strouthidis et al.15 In this analysis, an LRA was performed for each of the six tomograph-pre-defined sectors. Variability of the patients’ image series was determined by calculating the standard deviation of the residuals (BSD) and ranking these in order of magnitude within each sector. BSDs less than the 50th percentile were defined as having low variability and those greater than the 50th percentile as having high variability. The significance criterion for RA slope was determined by the variability of the image series. Change in any sector was defined when the slope exceeded 1% of baseline RA per year, with a significance P < 0.01 for low-variability series and P < 0.001 for high-variability series. Sectors were classified as progressing, improving, or stable based on a negative, positive, or nonsignificant slope, respectively. The estimated specificity is between 95.2% and 98.2%.15 To detect change adequately with this technique, patients with fewer than five contour-lined MT images in their series were excluded from the study.15

Visual Field Analysis

Point-wise linear regression analysis (PLRA) was used to analyze each patient’s VF series (Progressor software, ver. 3.0; Moorfields Eye Hospital/Medisoft Ltd., Leeds, UK) by a second observer (AS).8 The standard PLRA defines significant change as a change ≥1 dB per year for a central point and ≥2 dB for an edge point at the P < 0.01 level. For this study the three-omitting analysis was used, as it has been shown to have greater specificity than the standard PLRA technique.20 A full description of the technique is described elsewhere,20 but to summarize, consider a patient with five fields in the series, numbered n1 through n5. PLRA is applied to each point within the patient’s VF series after removal of the last two VFIs (i.e., n1–n3). If a point satisfies the standard Progressor criteria, the last field of the sequence is omitted, and the next field added and the slope is reconstructed (n1, n2, n4). If the slope again satisfies standard criteria, both the original end test field and the next field are omitted, and the slope is reconstructed with the final field of the series (n1, n2, and n5). If the slope still satisfies the standard criteria, the VF is said to be progressing. Using these criteria, the estimated specificity is between 95.2% and 98.2%.15 It has been shown that a reliable measure of longitudinal VF change is obtained in series with at least three VF tests per year over a 3-year period.9,21,22 Therefore, patients with less than nine VF tests in their series were excluded from the study.

Optic Nerve Head and VF Concordance of Change

In cases in which patients showed changes in both ONH and VF, congruity between sectors was assessed with an anatomic map designed to compare the relationship between HFA 24-2 test points and regions of the ONH.23 If an eye showed ONH progression in the same sector as VF progression, it was defined as showing ONH and VF congruency. If more than one ONH or VF sector showed progression, congruence was required in at least one sector. A further analysis was undertaken to consider the uneven distribution of HFA test points within each disc/field sector of the map. For example, the nasal disc sector is represented by 4 HFA test points, whereas the inferotemporal disc sector is represented by 13 HFA test points.23 For an even distribution, each disc sector would be represented by 8.67 HFA test points (8.67 × 6 disc sectors = 52 HFA test points). Weighting of the VF representation within an individual disc sector was determined by dividing the actual number of HFA test points by 8.67 to provide a weighted value (Table 1). In the second, weighted analysis, if a patient showed change within a VF sector, the number of points changing would be multiplied by the weighting index to generate a weighted change score. The VF sector was said to exhibit change if this score was ≥1.

IOP Analysis

Studies have suggested that a lower IOP level,7 reduced IOP fluctuation,24–26 and percentage of IOP reduction27 are all important in slowing the progression of VF defects in glaucoma. Therefore, for each patient the following IOP characteristics were determined:

1. Median IOP level over the follow-up period.
2. Variability of IOP level during the follow-up period (calculated

Table 1. Weighting Index to Compensate for Unequal Distribution of HFA Test Points in Each Disc Sector within the Anatomical Map23

<table>
<thead>
<tr>
<th>VF Sector Corresponding to Disc</th>
<th>Number of Points Tested in the 24–2 Strategy</th>
<th>Weighting Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferonasal</td>
<td>8</td>
<td>1.08</td>
</tr>
<tr>
<td>Inferotemporal</td>
<td>13</td>
<td>0.67</td>
</tr>
<tr>
<td>Superotemporal</td>
<td>10</td>
<td>0.87</td>
</tr>
<tr>
<td>Superonasal</td>
<td>11</td>
<td>0.79</td>
</tr>
<tr>
<td>Temporal</td>
<td>6</td>
<td>1.45</td>
</tr>
<tr>
<td>Nasal</td>
<td>4</td>
<td>2.17</td>
</tr>
</tbody>
</table>

A change in one point in the VF corresponding to the nasal disc sector would have greater weight than a change in one point in the inferotemporal sector. Changes in at least two points in the inferotemporal, superotemporal, and superonasal VF sectors are necessary for it to be considered true change.
RESULTS

Two hundred fifty patients of the original study cohort were included in the present study. Reasons for exclusion were: no preoperative or poor-quality preoperative HRT images (n = 21), fewer than five HRT images in the patient series or misalignment of the contour line in follow-up MT images that could not be corrected by manual alignment facility (n = 84), and fewer than nine VF tests in the patient series. Table 2 compares the number of patients showing congruity in location of progression.

Table 2. Demographics of the Study Cohort, Illustrating Differences in Baseline Characteristics in Patients Included in and Those Excluded from the Present Study

<table>
<thead>
<tr>
<th>Included (n = 250)</th>
<th>Excluded (n = 119)</th>
<th>Mann-Whitney U Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.8 (40 to 84)</td>
<td>71.6 (45 to 89)</td>
</tr>
<tr>
<td>Preoperative mean defect (dB)</td>
<td>-8.0 (-30.9 to -0.2)</td>
<td>-9.1 (-29.7 to -0.5)</td>
</tr>
<tr>
<td>Preoperative corrected PSD (dB)</td>
<td>6.3 (0.5 to 16.0)</td>
<td>6.9 (0.3 to 15.4)</td>
</tr>
<tr>
<td>IOP at preoperative visit (mmHg)</td>
<td>22.0 (14.3 to 38.5)</td>
<td>22.0 (14.5 to 49)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>99 (40)</td>
<td>40 (34)</td>
</tr>
<tr>
<td>Right eyes, n (%)</td>
<td>128 (51)</td>
<td>60 (50)</td>
</tr>
<tr>
<td>Follow up (mo)</td>
<td>60 (56 to 86)</td>
<td>8 (5 to 13)</td>
</tr>
<tr>
<td>VF tests, n</td>
<td>16 (11 to 25)</td>
<td></td>
</tr>
</tbody>
</table>

Unless marked otherwise, data are the median (range).

by using the standard deviation of IOP measurements over this period.

3. Percentage reduction from baseline at each study visit from 12 weeks after surgery and the median percentage reduction in IOP over this period.

A nonparametric analysis was used to determine whether IOP features differed significantly in patients in whom glaucoma was shown to be progressing or not. Furthermore, a multiple variable logistic regression analysis that included median IOP level over follow-up, IOP, and percentage reduction in IOP was used to assess which IOP feature was significantly associated with progression by any method.

All statistics were performed with commercial software (SPSS ver. 14.0; SPSS Inc., IL).

ONH and VF Progression

Eighty-five (34%) patients were deemed to be progressors by trend-based analyses of HRT and/or VF over time. When the weighted index was applied to VF analysis, this number decreased to 70 (28%) patients. Table 3 compares the number of patients progressing by HRT and VF examination methods and shows that the most of the progressors were detected by VF examination (~50% of progressors with both standard and weighted techniques).

Progression was detected by both VF and ONH in 16 patients (19% of progressors) with the three-omitting PLRA technique and 5 patients (21%) with the weighted PLRA technique. However, the congruity of HRT and VF sector change was found in approximately half of these patients.

The analysis suggests that using the weighted-VF method for determining change had little effect on the number of patients deemed to be progressors by both HRT and VF methods, nor on the congruity of agreement between sectors. However, it did significantly reduce the number of patients shown to be progressing by VF alone.

Table 3 displays the median number of progressing VF test locations within each group (VF alone and both VF and ONH). Use of the weighted analysis flagged patients who showed progression in more than one VF test location.

IOP Characteristics

Examination of the IOP characteristics of patients who progressed and did not progress (Table 5A) and further examination of the four groups (no progression, progression by HRT alone, by weighted-PLRA alone, and progression detected by both methods; Table 5B) showed no significant difference in baseline characteristics. However, median IOP over follow-up and IOP variability were greater in patients who showed progression. Patients showing no progression had significantly greater median percentage IOP reduction over their duration of follow-up compared with those who were deemed to be progressing by both HRT and weighted-PLRA methods (~39% reduction in nonprogressors compared with 23% IOP reduction in those progressing by both HRT and weighted-PLRA; Fig. 1). In the multivariate logistic regression analysis that included all three IOP characteristics, only IOP variability, defined as the standard deviation of IOP measurements over the follow-up period, remained a statistically significant factor associated with progression (adjusted odds ratio, 1.31; 95% confidence limit, 1.01–1.69). The analysis suggests that the most of the progressors were detected by VF examination (~50% of progressors with both standard and weighted techniques).

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patients was sometimes of insufficient quality to be included in the analysis, possibly because of the presence of cataract and slightly older age than those who were included. As HRT image quality is likely to be affected by the presence of cataract and other factors, the prevalence of cataract increases with advancing age,28 it is possible that worse IOP control may result in progression of glaucoma as detected by both HRT and weighted PLRA. The general consensus is that that three VF tests per year should provide sufficient sensitivity and specificity for detection of true change,9,21,22 a rate of testing followed by the 5-FU study protocol.

The rate of change in VF and global ONH RA was greatest in those patients displaying progression in both VF and ONH. Examination of IOP variability over the follow-up period, suggesting that worse IOP control results in progression of disc and field defects. Progressors were slightly older than nonprogressors, but the differences only approached significance. Data are median values for each group. Mann-Whitney U test for ranked differences.

### Table 5A. Baseline Characteristics, IOP Levels and IOP Reduction in Progressing and Nonprogressing Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Progression (n = 185)</th>
<th>Progression (n = 70)</th>
<th>Mann-Whitney U Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66 (59 to 72)</td>
<td>69 (62 to 75)</td>
<td>0.06</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>59.9 (48.1 to 70.7)</td>
<td>60.3 (48.0 to 69.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>Baseline MD (dB)</td>
<td>−7.8 (−16.3 to −3.8)</td>
<td>−8.7 (−15.8 to −4.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>Preoperative IOP (mm Hg)</td>
<td>22.3 (20.3 to 24.5)</td>
<td>21.5 (20.3 to 24.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Median IOP level over follow-up (mm Hg)</td>
<td>14.0 (11.8 to 16.0)</td>
<td>15.1 (12.7 to 17.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median percentage IOP reduction over follow-up (%)</td>
<td>−38.4 (−51.8 to −26.4)</td>
<td>−31.4 (−43.1 to −21.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>IOP variability over follow-up: SD of measurements (mm Hg)</td>
<td>2.3 (1.7 to 2.9)</td>
<td>2.5 (1.8 to 3.6)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients within each group were similar. However, there were significant differences between median IOP, percentage reduction, and IOP variability over the follow-up period, suggesting that worse IOP control results in progression of disc and field defects. Progressors were slightly older than nonprogressors, but the differences only approached significance. Data are median values for each group. Mann-Whitney U test for ranked differences.

### Table 5B. Baseline Characteristics, Slope of Change, IOP Levels, and IOP Reduction in Each Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Progression (n = 185)</th>
<th>HRT Only (n = 20)</th>
<th>VF Only (n = 35)</th>
<th>Both HRT and VF (n = 15)</th>
<th>Kruskal-Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66 (59 to 72)</td>
<td>66 (59 to 71)</td>
<td>71 (62 to 76)</td>
<td>69 (62 to 75)</td>
<td>0.11</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>58.5 (48.1 to 69.7)</td>
<td>54.6 (43.8 to 72.7)</td>
<td>60.9 (48.8 to 68.4)</td>
<td>60.3 (47.6 to 66.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>Baseline MD (dB)</td>
<td>−7.8 (−16.2 to −3.8)</td>
<td>−5.5 (−12.7 to −3.0)</td>
<td>−9.7 (−16.2 to −4.5)</td>
<td>−8.9 (−13.8 to −5.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Preop IOP (mm Hg)</td>
<td>22.3 (20.3 to 24.5)</td>
<td>22.0 (20.6 to 25.4)</td>
<td>23.0 (20.5 to 24.8)</td>
<td>21.5 (19.5 to 22.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Slope of global RA change over follow-up (% RA per year)</td>
<td>0.2 (−1.4 to 3.5)</td>
<td>−3.6 (−6.5 to −1.8)</td>
<td>0.1 (−1.4 to 2.0)</td>
<td>−5.3 (−6.3 to −2.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean slope over follow-up (dB per year)</td>
<td>0.0 (−0.3 to 0.2)</td>
<td>−0.1 (−0.4 to 0.1)</td>
<td>−0.6 (−1.1 to −0.3)</td>
<td>−1.0 (−1.2 to −0.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median IOP level over follow-up (mm Hg)</td>
<td>14.0 (11.8 to 16.0)</td>
<td>15.1 (14.0 to 16.9)</td>
<td>14.3 (10.3 to 16.5)</td>
<td>16.5 (13.5 to 17.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median percentage IOP reduction over follow-up (%)</td>
<td>−38.7 (−52.0 to −27.3)</td>
<td>−30.6 (−39.1 to −20.6)</td>
<td>−37.1 (−52.5 to −23.9)</td>
<td>−23.3 (−31.6 to −11.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>IOP variability over follow-up: SD of measurements (mm Hg)</td>
<td>2.3 (1.7 to 2.9)</td>
<td>2.2 (1.6 to 3.6)</td>
<td>2.5 (1.9 to 3.5)</td>
<td>3.1 (2.4 to 4.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The rate of change in VF and global ONH RA were greatest in those patients displaying progression in both VF and ONH. Examination of IOP characteristics within each group show differences between median IOP, percentage reduction, and IOP variability over the follow-up period. The data suggest that worse IOP control may result in progression of glaucoma as detected by both HRT and weighted PLRA. Data shown are median (IQR) for each group. Kruskal-Wallis one-way analysis of variance to test rank differences between groups.
In a study by Strouthidis et al., of HRT and VF longitudinal data of 198 ocular hypertensive (OHT) patients over a median follow-up of 6 years, approximately 9% of eyes displayed progression by ONH structure alone, 15% by VF alone, and 3.5% by both techniques. Congruity of ONH and VF sectoral change was displayed in all eyes. In our study, sectoral congruity was found only in half of the eyes displaying both ONH and VF change. The difference may be explained by the populations studied; our cohort consisted of eyes with established and somewhat advanced glaucoma. It is possible that in eyes with advanced disease, changes in ONH structure may be more difficult to detect, although this theory should be explored further. In another longitudinal study of 77 patients with glaucoma followed up for a median of 5.5 years, only 33% of progressors displayed changes by both the ONH and VF methods, although the respective false-positive rates for detection by these methods were not reported. The lack of agreement between structural ONH and VF functional change in progressive glaucoma is not an uncommon finding. The disparity is likely to be in part due to the differing levels of measurement noise displayed by the devices used to detect change, and it has been suggested that structural and functional methods be considered as independent indicators of glaucoma damage.

The present study also examined the levels of IOP after trabeculectomy in patients with progression compared with those showing no progression, and found that less IOP reduction and a greater postoperative IOP variability was displayed by eyes showing progression in both the ONH structural and VF functional methods. This result is in agreement with those in most studies in which the effects of IOP level on progression of glaucoma have been examined. A lower follow-up IOP reduces the risk of progression of VF defects in patients with established glaucoma, and delays progression in patients with newly diagnosed disease. In our study, patients showing ONH and VF changes had significantly higher median IOP over follow up compared with nonprogressors (16.5 mm Hg compared with 14 mm Hg), and less IOP reduction from baseline values (23% vs. 39% median reduction over the follow-up period).

The role of IOP variability in glaucomatous progression has also been studied. Patients exhibiting large diurnal fluctuations in IOP are at increased risk of development of progressive glaucomatous damage. Large variations in intervisit IOP measurements, defined as either the standard deviation of IOP measurements or range of IOP over follow-up, have also been shown to be risk factors for glaucomatous progression in patients with newly diagnosed disease. Although some investigators have shown that IOP variability does not have an independent role in progression of the disease, our study showed that IOP variability was slightly higher in patients who progressed overall and that variability (defined as the standard deviation of intervisit IOP measurements) was greatest in eyes that showed changes in both ONH structure and VF sensitivity. Multiple logistic regression analysis also showed that IOP variability was significantly associated with progression of glaucoma, even after adjustment for both median IOP level and percentage IOP reduction. However, IOP variability was significantly associated with median level of IOP, and while statistically IOP variability was the only significant factor, we interpret these findings with a degree of caution. The data show a large degree of overlap of IOP characteristics between progressing and nonprogressing groups, suggesting they are but one factor to explain progression in individual patients. Furthermore, as part of study protocol, interventions (e.g., IOP lowering therapy and bleb needling) were introduced if the surgery was deemed to be failing. The presented analysis does not explicitly take into account such interventions, except by their effects on IOP characteristics over the follow-up period.
As such, although IOP variability was statistically the factor most associated with progression of glaucoma, from the presented analyses one cannot identify a causal link between IOP variability and progression. The aspect of IOP control and the role of further surgery such as bleb needling and cataract extraction after trabeculectomy will be explored in detail in a separate MoreFlow 5-FU study analysis.

There are some caveats regarding the conclusions of the present study. First, the influence of cataract on our findings has not been fully explored. Although we did not define a cutoff image quality for HRT image inclusion, only patients with at least five images within their series and adequate contour-lining were included. Indeed, the present study excluded 119 eyes for HRT image-quality reasons. This inclusion criterion would automatically exclude any images of poor quality that resulted in poor contour line alignment, and thus served as an indirect control for the presence of significant cataract. A criticism of PLRA is that it uses raw sensitivity values when assessing VF sensitivity over time and therefore may be affected by depressions in sensitivity caused by cataract. However, it is likely that any patients with significant cataract that affected HRT image quality would have been excluded from the VF analysis. The role of cataract in the 5-FU trial outcomes will be further discussed in another paper. Second, although progression was predominantly detected by changes in VF sensitivity in this cohort, it may be in part due to the disparity between the frequency of ONH imaging and VF testing, as well as the number of test points in each technique. Since there are a greater number of test points in the VF compared with the ONH (52 vs. 6 points, respectively), combined with a greater number of tests within the time series, it is possible that change is more likely to be detected in the VF series than in the ONH image series. Furthermore, the two testing modalities may exhibit different levels of measurement variability, or noise, that may mask or underestimate degrees of progression. However, the results of our study agree with most others that found a dissociation between changes in VF function and ONH structure in patients with ocular hypertension or glaucoma over relatively short periods. The measurement variability in the detection of true change is a subject for further exploration and was beyond the scope of this study.

To conclude, in our study, approximately one third of eyes continued to display glaucomatous progression after trabeculectomy, and that progression was detected predominantly by changes in VF sensitivity over ONH structure. Changes in both ONH structure and VF sensitivity are present in only a small proportion of eyes, with IOP appearing to be more poorly controlled in these eyes compared with those that show no change at all. This study provides further evidence of the importance of controlling IOP in inhibiting the progression of glaucoma, and the association will be further explored in a separate study.

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References


