Longitudinal and Cross-sectional Analyses of Visual Field Progression in Participants of the Ocular Hypertension Treatment Study

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Objective: To assess agreement between longitudinal and cross-sectional analyses for determining visual field progression in data from the Ocular Hypertension Treatment Study.

Methods: Visual field data from 3088 eyes of 1570 participants (median follow-up, 7 years) were analyzed. Longitudinal analyses were performed using change probability with total and pattern deviation, and cross-sectional analyses were performed using the glaucoma hemifield test, corrected pattern standard deviation, and mean deviation. The rates of mean deviation and general height change were compared to estimate the degree of diffuse loss in emerging glaucoma.

Results: Agreement on progression in longitudinal and cross-sectional analyses ranged from 50% to 61% and remained nearly constant across a wide range of criteria. In contrast, agreement on absence of progression ranged from 97.0% to 99.7%, being highest for the stricter criteria. Analyses of pattern deviation were more conservative than analyses of total deviation, with a 3 to 5 times lesser incidence of progression. Most participants developing field loss had both diffuse and focal changes.

Conclusions: Despite considerable overall agreement, 40% to 50% of eyes identified as having progressed with either longitudinal or cross-sectional analyses were identified with only one of the analyses. Because diffuse change is part of early glaucomatous damage, pattern deviation analyses may underestimate progression in patients with ocular hypertension.

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Group Information: A list of the Ocular Hypertension Treatment Study Group is available at https://vrcc.wustl.edu.

The Ocular Hypertension Treatment Study (OHTS) demonstrated that treatment to lower intraocular pressure delays or prevents the development of glaucoma in ocular hypertension. In participants randomized to receive treatment, the 5-year incidence of glaucoma was 4.4%, approximately half of that observed in those who did not receive treatment (9.5%).[1,2]

In the OHTS, one end point for the development of glaucoma was the occurrence of reproducible visual field loss.[3] Initially, all participants had normal visual fields, defined by a glaucoma hemifield test (GHT)[4] and a corrected pattern standard deviation (CPSD) within normal limits.[3,5] If during follow-up either the GHT and/or the CPSD was outside normal limits in 3 consecutive tests, visual field progression was suspected, and the participant's visual fields were referred to the end point committee to confirm that progression attributable to glaucoma had occurred.[6] The GHT and CPSD summarize results from a single visual field examination by comparing the data with those of healthy individuals.[7] Because the GHT and CPSD are based on a comparison with normative data at a single point in time, this is a cross-sectional analysis, even though 3 consecutive visual fields may be required to confirm an abnormality. A different approach to measuring progression is to determine whether there is a significant change within the patient's visual field over time[8,9]; this is referred to as a longitudinal analysis. Several types of longitudinal analyses have been described to analyze either the entire follow-up (trend analysis, by linear regression)[10-13] or the baseline and a single follow-up examination (event analysis, by glaucoma change probability analysis).[13-15] Owing to the large range of normal values, a visual field may show evidence of change with longitudinal analysis while remaining within the normal limits with a cross-sectional analysis. Therefore, it is possible that longitudinal analyses reveal disease-related changes in different eyes than do cross-sectional analyses.

The primary objective of this article is to investigate the agreement between longitudinal and cross-sectional progression

analyses in participants of the OHTS. A second goal is to establish how a progression analysis applied in the Early Manifest Glaucoma Trial (EMGT)[16] to patients with established glaucoma performs in patients with ocular hypertension. These questions have important implications for how patients with ocular hypertension should be followed up in clinical practice and on the design of research studies that use visual field progression as an outcome measure.

METHODS

DATA SET

This research includes data obtained in the OHTS through July 31, 2003. The OHTS was a multicenter randomized clinical trial conducted in accord with the principles of the Declaration of Helsinki to determine the efficacy and safety of ocular hypotensive therapy in preventing or delaying the development of glaucoma in patients with ocular hypertension.[3]

All eligible participants had ocular hypertension and were monitored with static automated perimetry program 30-2 of the Humphrey Field Analyzer (Carl Zeiss Meditec, Inc, Dublin, California) with the full threshold strategy. For this article, only eyes with 2 normal baseline visual fields and at least 3 follow-up examinations were included. To be classified as normal, baseline fields had to have a GHT classification of "within normal limits" as well as CPSD and mean deviation (MD) within normal limits ($P > 10\%$).

A total of 3088 eyes of 1570 participants met these criteria. There were a mean of 15 (interquartile range, 5-18) visual field examinations per eye, obtained over a mean follow-up of 6.7 years (6.3-7.5 years). We elected not to exclude visual fields for nonreliability on the basis of fixation losses or false-positive or false-negative responses. Therefore, a small proportion (461 of 44 302, or 1.0%) of visual fields retained for this analysis had failed to meet the OHTS reliability criteria.[17]

ANALYSES

Cross-sectional Analysis

In the OHTS, visual field progression was suspected if the GHT classification became "outside normal limits" or "general reduction of sensitivity" in 3 consecutive examinations or if the CPSD became abnormal ($P < 5\%$) in 3 consecutive examinations. The same index had to be involved, and the spatial pattern of the defect had to be consistent across the 3 examinations.[6] For brevity, we refer to this as the "OHTS criterion." To be clear, meeting the OHTS criterion by itself had not constituted an end point in the OHTS; rather, it established a "suspicion of glaucomatous visual field progression" and triggered subsequent review by the end point committee, which, by consensus, determined whether the eye had unequivocally developed glaucoma. For this reason, not all eyes fulfilling the OHTS criterion were confirmed as having a glaucomatous change by the end point committee.

There is no reference standard for what degree or type of visual field change constitutes a definite increment of glaucomatous damage, making it difficult to determine empirically the sensitivity and specificity of progression analyses. To arrive at a meaningful assessment of the agreement between the 2 different types of analysis, independent of the trade-off between sensitivity and specificity governed by a particular criterion, we elected to equalize the progression rates of the longitudinal and cross-sectional analyses.

To vary the number of eyes classified as progressing with the cross-sectional approach, we established a range of criteria that were similar to the OHTS criterion but identified progression in a smaller or larger number of eyes. A cross-sectional score was assigned as follows. For each test, GHT classifications of "borderline," "outside normal limits," or "general reduction in sensitivity" were assigned a score of 1. Each of the MD and CPSD indices with significant *P* values at less than 5% or less than 10% was assigned a score of 1, and at *P* less than 2%, each was assigned a score of 2. For each test, the scores were summed with the results of the previous 2 tests such that each test was given a score ranging from 0 to 15. By varying the criterion, a more than 10-fold variation in progression rates with cross-sectional analyses could be achieved.

Longitudinal Analysis

Change probability analyses of progression were performed to measure visual field change over time.[13] These analyses compare the deviation at each test location of the follow-up field to the average value obtained at 2 baseline examinations. Test locations at which the deviation is outside the 5th percentile of retest variability established in a group of patients with stable glaucoma are flagged for likely deterioration, and progressive change in a visual field is determined based on the number of locations that show deterioration in 3 consecutive examinations. These analyses were performed with total deviation and pattern deviation values and custom-written software previously described.[13] The pattern deviation analyses are equivalent to the Guided Progression Analysis of the Statpac software (Carl Zeiss Meditec, Inc),[15] whereas the total deviation analyses are equivalent to the older Glaucoma Change Probability analysis.[7] The criteria of the longitudinal analyses were varied by adjusting the number of test locations that had to show significant change in 3 consecutive examinations.

Agreement Between Longitudinal and Cross-sectional Analyses

We assessed the agreement between longitudinal and cross-sectional analyses with total deviation change analysis and cross-sectional score as described previously. Criteria were selected such that approximately the same number of eyes was classified as having progressed with each type of analysis. Three criteria (liberal, moderate, and conservative) were established in this manner. Agreement between longitudinal and cross-sectional analyses for progressing and nonprogressing eyes was determined[18] and visualized by area-proportional Venn diagrams.

Comparison Between Total Deviation and Pattern Deviation Analyses

In the EMGT, change probability analyses were performed with pattern deviation rather than total deviation values to guard against the effect of diffuse visual field loss from developing cataract. We, therefore, compared the incidence of progression between total deviation and pattern deviation analyses, with criteria of at least 2, 3, 5, and 8 test locations, with significant change in 3 consecutive examinations. To determine the role of diffuse visual field loss, changes over time in the MD were compared with those of the general height (GH) of the visual field. The GH is defined as the 85th percentile of the ranked total deviation values and is an index of sensitivity at the "least damaged" points in the visual field.

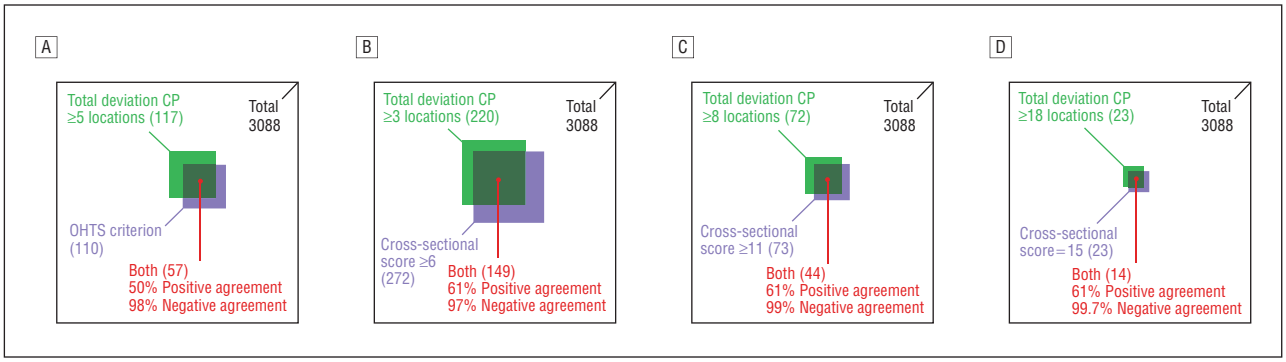

Figure 1. Proportion of positive agreement between longitudinal and cross-sectional analyses across a wide range of criteria. The area of each square and overlap is proportional to the number of eyes classified as having progressed using each method (in parentheses). The large square (black) represents the total number of eyes (n=3088). A, Agreement between longitudinal (total deviation change probability [CP], green square) and cross-sectional analyses (Ocular Hypertension Treatment Study [OHTS] criterion, lavender square) of visual field progression. The area of each square, and their overlap, is proportional to the number of eyes classified as having progressed with each method (in parentheses).The total deviation criterion (5 locations) has been selected to provide the best possible match to the incidence of change with the OHTS criterion. Agreement between longitudinal (total deviation, green square) and cross-sectional (lavender square) analyses of visual field progression with liberal (B), moderate (C), and conservative (D) criteria approximately matched for incidence of progression.

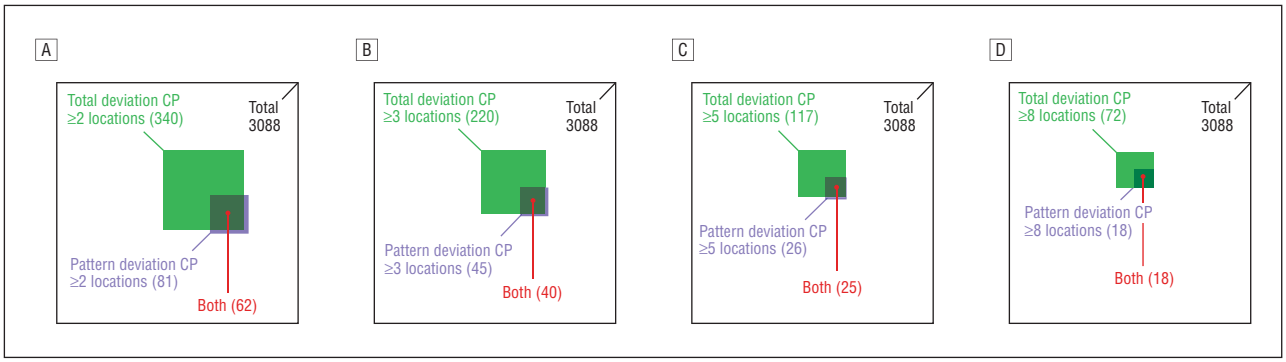

Figure 2. Agreement between total deviation (green squares) and pattern deviation (lavender squares) change probability (CP) analyses of visual field progression. The area of each square, and overlap is proportional to the number of eyes classified as having progressed using each method (in parentheses). The large square (black) symbolizes the total number of eyes (n=3088). A, Results using criteria of at least 2 (A), 3 (B), 5 (C), and 8 (D) locations with significant change in 3 consecutive tests.

This index is used for calculation of the pattern deviation values, and changes in the GH reflect diffuse changes in the visual field.

RESULTS

Of the 3088 eyes included in the study, 110 (3.6%) met the OHTS criterion for suspected visual field progression. In the total deviation change probability analysis, this number was matched closest by a criterion of 5 test locations that detected progression in 117 eyes. The analyses agreed on the presence of progression in 57 eyes and on its absence in 2918 eyes, giving rise to proportions of positive and negative agreement of 50% and 98%, respectively (**Figure 1**A).

The proportion of positive agreement between longitudinal and cross-sectional analyses remained similar across a wide range of criteria (Figure 1B-D). A less conservative criterion (total deviation change in ≥3 locations and a cross-sectional score of ≥6) identified progression in more than 10 times as many eyes as a more conservative criterion (total deviation change in ≥18 locations and a cross-sectional score of 15), but the proportion of positive agreement was identical (61%) for the liberal, moderate, and conservative criteria.

Analyses of pattern deviation classified considerably fewer eyes as having progressed than did analyses with total deviation. For example, with a criterion of at least 3 locations, total deviation analyses identified progression in 220 eyes, whereas pattern deviation analyses identified progression in only 45 eyes. Almost all eyes identified with pattern deviation analyses were identified with total deviation analyses also (**Figure 2**).

To investigate the large differences between total deviation and pattern deviation analyses, we compared the rates of change of the MD and GH indices in all eyes in which the end point committee had ascertained a glaucomatous end point, either by visual field or optic disc change (**Figure 3**). With purely focal visual field change, the MD would show a negative slope, whereas the slope of the GH would be close to zero. In contrast, with purely diffuse visual field change, the slopes of MD and GH would both be negative and similar to each other. This analysis showed that most eyes with glaucomatous end points exhibited diffuse as well as focal visual field changes.

COMMENT

In patients who develop glaucoma from ocular hypertension, both longitudinal and cross-sectional ap-

proaches to detecting progression have a sound rationale. However, although the properties of both approaches have been investigated in healthy subjects and in patients with glaucoma,[13,16,19] they have not previously been compared in patients with ocular hypertension. In a previous study,[13] we demonstrated the high specificity of change probability analysis, based on either total or pattern deviation, in a group of patients with glaucoma and healthy subjects observed for up to 13 years. With the EMGT criterion, for example, the 5-year "progression" rate in healthy individuals was 1% to 2%. Findings of progression with these analyses, therefore, constitute a credible signal that real change has occurred.

The primary aim of this article was to investigate the agreement between longitudinal and cross-sectional analyses of visual field progression in patients with ocular hypertension and to establish whether these analyses detect progression in different eyes. These findings indicate that almost all eyes classified as stable with one type of analysis were also classified as stable with the other, whereas only 50% to 60% of the eyes classified as having changed with either longitudinal or cross-sectional analyses were identified by both approaches. The finding of close agreement on the absence of progression (>97%) was expected given the low incidence of glaucoma and the application of highly specific tests for progression. Even with the liberal criteria, most eyes did not show progression with either longitudinal or cross-sectional analyses.

However, the modest proportion of agreement on the presence of progression (50%-61%) means that many eyes were identified as having changed with one analysis but not with the other. One plausible explanation for this finding is that the 2 types of analysis identify different aspects of visual field change. For example, the longitudinal analyses performed in this study identified localized changes at individual test locations, whereas the cross-sectional analyses of GHT and CPSD operated on hemifield sectors and the global visual field, respectively.

Because the recent clinical trials in glaucoma have all used different analyses and different criteria for establishing end points of visual field progression, it is difficult to compare progression across these studies. The EMGT approach has previously been investigated by several groups and is now incorporated into the Guided Progression Analysis of the HFA Statpac software. When we applied the EMGT criteria[16] to the participants of the OHTS, pattern deviation analyses were considerably more conservative than those with total deviation, and the differences were larger than those reported in patients with established glaucoma.[13,20] To explain these unexpectedly large differences between total deviation and pattern deviation analyses, we compared the rates of MD and GH change over time. In almost all participants who developed glaucoma, changes in GH occurred alongside changes in MD, indicating that purely focal progression in glaucoma is rare, at least when glaucomatous damage first emerges in patients with high intraocular pressure. Because pattern deviation analyses discount any diffuse changes of the visual field, they underestimate the overall amount of glaucoma-related change. Exclusive reliance on pattern deviation analyses may, therefore, underestimate the true incidence of early glaucomatous progression.

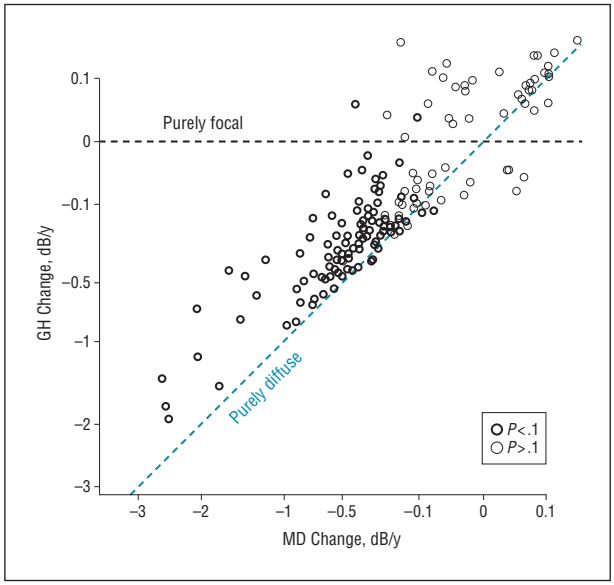

Figure 3. Changes in visual field general height (GH) and mean deviation (MD) in eyes that developed glaucoma. Changes were established as the slope (by linear regression) of GH and MD with follow-up time. Eyes with purely focal change would show a change in MD but not in GH (dashed horizontal line), while eyes with purely diffuse change would show approximately equal slopes with both indices (dashed diagonal line). Most eyes showed focal and diffuse changes.

With visual field progression, there is no independent reference standard for what magnitude or type of change best separates true progression from variability. Sensitive criteria will identify most eyes with genuine worsening of the disease but will also misidentify cases in which no such change had really taken place (lower specificity). More conservative criteria provide greater specificity to true change but miss a greater number of eyes with more subtle progression. Each progression criterion provides a unique trade-off between sensitivity and specificity, and the choice of a particular criterion depends largely on the setting in which it is to be applied. Frequency of examinations, quality of data, and incidence of progression all differ between clinical practice, epidemiologic studies, and treatment trials, and no single progression criterion is likely to be equally useful across the large spectrum of circumstances and requirements. However, the overall agreement between longitudinal and cross-sectional analyses in this research remained consistent over an approximately 10-fold variation in progression rates, and the finding that longitudinal and cross-sectional criteria identify progression in different subsets of eyes is, therefore, relevant to a wide range of clinical settings in which patients with ocular hypertension might be observed. A key message of the current article is that longitudinal analyses should be considered a complement to cross-sectional analyses of visual field progression when patients with ocular hypertension are observed in clinical practice.

In summary, there was reasonable agreement between longitudinal and cross-sectional analyses of pro-

gression in participants in the OHTS when the criterion for each was adjusted to identify the same number of progressive eyes. However, a substantial number of eyes were identified as having changed with only one analysis but not the other, and the results of longitudinal analyses of visual field progression should, therefore, be considered alongside single field analyses when patients at risk for developing glaucoma are observed over time. Finally, diffuse change appears to be an integral part of visual field progression in early glaucoma, and analyses relying solely on pattern deviation to detect progression may significantly underestimate the true incidence of emerging glaucoma in eyes with ocular hypertension.

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