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Long-term progression at individual mean intraocular pressure levels in primary open-angle and exfoliative glaucoma

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PURPOSE. *To describe progression and non-progression rates at individual mean intraocular pressure (IOP) levels for patients with primary open-angle and exfoliative glaucoma.*
METHODS. *A meta-analysis of five previously published retrospective studies describing progression and non-progression rates at individual intraocular pressure levels over 5 or more years of follow-up. All patients had primary open-angle (four studies) or exfoliative glaucoma (one study).*
RESULTS. *This meta-analysis included 822 patients of whom 655 (80%) had primary open-angle glaucoma and 167 (20%) had exfoliative glaucoma. In total, 220 patients progressed (27%), while 602 (73%) remained stable over 5 years. The mean IOP was 20.0 for progressed and 17.1 mmHg for stable patients (p=0.0004). The peak IOP was 29.1 for progressed and 23.6 mmHg for stable patients (p=0.0014). At an IOP level >18 mmHg, 49% of patients remained stable; at 18 mmHg, 78%; between 13 and 17 mmHg, 82%; and <13 mmHg, 96%. Additional factors associated with progression were older age (p=0.0004) and exfoliative glaucoma (p=0.0001). However, multivariant regression analysis identified only mean IOP as a risk factor for progression (p=0.039).*
CONCLUSIONS. *This study suggests that maintaining an IOP well within the normal range over 5 years in patients with primary open-angle or exfoliative glaucoma helps to prevent glaucomatous progression. (Eur J Ophthalmol 2008; 18: 765-70)*

KEY WORDS. *Intraocular pressure, Primary open-angle glaucoma, Exfoliative glaucoma, Progression, Meta-analysis*

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INTRODUCTION

Over the past few years, several excellent multicenter studies, sponsored by the National Institutes of Health, have helped confirm the importance of reducing intraocular pressure (IOP) to help prevent glaucomatous progression in ocular hypertensive and primary open-angle glaucoma. Most of these trials expressed their treatment effect in terms of percent reduction of IOP (1-4). In contrast, the AGIS study provided progression rates based

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on four levels of mean IOP combined with their associated peak IOP (5).

Despite the pressure reduction achieved in these trials, many patients still had glaucomatous progression. The exact reasons why some patients still progressed, although a therapeutic decrease in pressure was achieved, were not clear by the study results. The trials were designed to demonstrate the benefit of treatment, or a specific type of treatment, and not to determine specific treatment goals. Consequently, despite these important studies, data are needed to better describe progression rates at individual levels of mean IOP. Such data might better clarify appropriate target levels for patients with ocular hypertensive and primary open-angle glaucoma.

Over the past several years a number of studies have been published that evaluated the long-term progression rates of individual mean pressure levels of patients with primary open-angle and exfoliative glaucoma (6-10). The design of these studies was similar in each case allowing for the results to be combined.

The purpose of this meta-analysis was to evaluate progression and non-progression rates at individual mean IOP levels for patients with primary open-angle and exfoliative glaucoma.

METHODS

We included in this study known articles of the authors that met the inclusion criteria. We also performed a search on PubMed for additional articles that met the criteria using the key words intraocular pressure, glaucoma, primary open-angle, exfoliative/pseudo-exfoliative glaucoma, long-term outcomes, progression, and stability.

Included articles in this meta-analysis were studies that met the following criteria: long-term progression and non-progression rates were described at individual levels of IOP, patients were chosen in a non-biased fashion (randomized or from consecutive charts) and included patients with primary open-angle or exfoliative glaucoma. Exfoliative patients were allowed in this meta-analysis after it was shown that the pressure levels that best prevented over two thirds of patients from progression (17 mmHg) was within the range of the four included primary open-angle glaucoma studies (16–21 mmHg). Glaucoma diagnoses (primary open-angle or exfoliative) were made generally based on typical glaucomatous optic disc (neural rim thinning or notching, saucerization, thin nasal rim, or total cupping) and/or visual field changes (typical nerve fiber layer changes: nasal step or paracentral, Seidel or arcuate scotoma). Exfoliative patients must have demonstrated typical anterior segment findings of exfoliative syndrome (11).

Included studies must also have met the following requirements for data collection: begun from the patient's initial examination with the study investigator, data was gathered regarding stable glaucoma for up to 5 years, recorded pressures by Goldmann applanation tonometry, available routine follow-up visits typically every 3–6 months and dilated optic disc and visual field examinations approximately every year, optic disc examinations by stereoscopic techniques, the same investigator at each clinical site evaluated each patient during the follow-up period, and included only one randomly chosen eye.

In addition, in included studies glaucomatous progression must have been determined clinically by the investigator based on both the visual field and the optic disc, noted in the chart with the associated reason or determined by a separate reading center and having a reason for data collection to discontinue. Data were not recorded after the time of progression so the information included in this meta-analysis would reflect the ocular condition that worsened glaucoma. Generally, criteria for progression were an increase in thinning of the neural rim or a worsening of glaucomatous visual field loss. Patients without progression noted were assumed to be stable.

Statistics

The numbers of patients who were either stable or progressed over 5 years were calculated for each level of IOP. These data were not analyzed statistically but are described.

Statistical analyses were performed between patients who were either stable or progressed. All data were two-sided and unpaired. A value of 0.05 was selected to determinate statistical significance. All parameters included in all five studies were analyzed in the meta-analysis.

A Stouffer combined test was used where a Student *t*-test was performed in the original article between groups to analyze data for patient age and mean as well as peak IOPs (12-14). A chi-square test was used to analyze differences between groups of non-ordered scores: diagnosis, gender, and race. Only one eye from each patient, which was chosen in each original study, was analyzed in this meta-analysis.

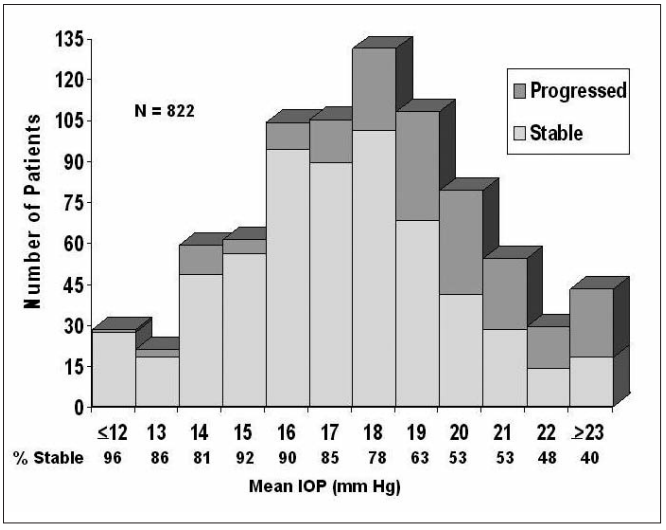

Fig. 1 - *The number of patients in the five studies included in the meta-analysis who were stable at mean intraocular pressure levels over 5 years. The numbers below the intraocular pressures indicate the percent of patients who remained stable at each mean intraocular pressure level from 13 to 22 mmHg and <12 and >23 mmHg.*

Bias was assessed and reduced by evaluating homogeneity by the Rosenthal diffuse test (14). A z-score above 1.96 was used as the upper level that would initiate eliminating studies that caused a lack of homogeneity. Also, we weighted the z-scores within the Stouffer tests by the size of the sample from the original article by using the method of Mosteller and Bush (14).

We used a multivariant regression analysis to analyze for independent risk factors for progression of glaucoma in this study. Because individual databases were not available, the analysis was performed as a sample of n = 5 using the combined patients characteristics derived from the meta-analysis.

RESULTS

This current meta-analysis included 822 patients in which 655 had primary open-angle and 167 had exfoliative glaucoma. Of these, 373 were male and 449 were female; 591

TABLE I - PATIENT CHARACTERISTICS FOR EACH STUDY INCLUDED IN THE META-ANALYSIS

	Ref. 6		Ref. 7		Ref. 8		Ref. 9		Ref. 10		Total			p value
	P	S	P	S	P	S	P	S	P	S	P	S	All	
n	28	27	16	56	34	184	82	85	60	250	220	602	822	
Diagnosis														
POAG	28	27	16	56	34	184	0	0	60	250	138	517	655	0.0001
EXG	0	0	0	0	0	0	82	85	0	0	82	85	167	
Gender														
Male	10	9	6	20	12	82	41	40	28	125	97	276	373	0.65
Female	18	18	10	36	22	102	41	45	32	125	123	326	449	
Race														
Caucasian	27	24	2	10	22	125	82	85	38	176	171	420	591	0.08
Black	1	3	14	46	10	45	0	0	20	71	45	165	210	
Other	0	0	0	0	2	14	0	0	2	3	4	17	21	
Age, yrs	72.2	62.8	61.2	71.5	70.4	65.4	74.0	75.0	61.6	60.2	67.9	67.0	67.4	0.0004

P = Progressed; S = Stable; POAG = Primary open-angle glaucoma; EXG = Exfoliative glaucoma

TABLE II - FOLLOW-UP DATA FOR EACH STUDY INCLUDED IN THE META-ANALYSIS

	Ref. 6		Ref. 7		Ref. 8		Ref. 9		Ref. 10		Total			p value
	P	S	P	S	P	S	P	S	P	S	P	S	All	
n	28	27	16	56	34	184	82	85	60	250	220	602	822	
Mean IOP	20.4	17.5	21.3	15.4	19.5	17.2	20.1	18.1	18.5	17.2	20.0	17.1	18.5	0.0004
Peak IOP	27.2	22.8	39.2	24.5	27.5	23.9	29.2	24.1	22.6	22.5	29.1	23.6	26.4	0.0014

P = Progressed; S = Stable; IOP = Intraocular pressure

TABLE III - MULTIVARIANT STEPWISE REGRESSION

Factor	p value
Glaucoma diagnosis	0.311
Gender	0.8362
Race	0.199
Age	0.2543
Mean intraocular pressure	0.0392
Peak intraocular pressure	0.9137

were Caucasian, 210 were African American, 3 were Hispanic, 3 were Asian, 1 was East Indian, and 14 were unknown. The average age was 67.4±12.5 years. In all, 220 patients progressed, while 602 remained stable over a mean follow-up period of 4.7±2.3 years. Table I shows these patient characteristics divided between those individuals who were progressed or stable for each individual study. Patients who were older (p=0.0004) or had exfoliative glaucoma (p=0.0001) were more likely to have glaucomatous progression.

Follow-up data over the 5 years are shown in Table II. A lower pressure for both the mean (p=0.0004) and peak (p=0.0014) pressure, weighted for sample size, was observed with stable patients.

The results of the number of progressed and stable patients, at each IOP level, are shown in Figure 1. In general, at IOPs >18 mmHg, 49% of patients remained stable. At 18 mmHg, 78% remained stable; between 13 and 17 mmHg, ≥82% remained stable; and at pressures <13 mmHg, 96% remained stable.

The results of the multivariant regression analysis are shown in Table III. Only the mean IOP was identified as an independent risk factor for progression (p=0.039).

The test for homogeneity for the mean IOP showed a chi-square score of 0.74 (p=0.95). Consequently, the mean IOP results for each of the studies were thought to be homogenous.

DISCUSSION

Controversy still exists over the proper treatment endpoints of patients with glaucoma. Several historical and recent studies have demonstrated not only the benefit of IOP reduction in primary open-angle glaucoma, but have indicated specific target IOPs that help prevent progressive glaucomatous damage. These reports have implied that approximately 5–15% of patients with moderate or advanced glaucomatous damage usually progressed with a mean IOP of between 13 and 18 mmHg over 5 years (5, 7, 8, 15-20). Several studies, however, have indicated a further benefit in patients with advanced glaucoma with IOPs as low as 12–13 mmHg (5, 17, 19).

Recently Konstas et al evaluated the long-term target IOPs required to prevent progression in patients with exfoliative glaucoma (7). This study found that IOPs ≤17 mmHg best help prevent progression, although the percent of patients who progressed had higher IOP levels than typically found in patients with primary open-angle glaucoma.

Why some patients who were controlled with ≤18 mmHg continued to progress is not precisely known. Although genetic and vascular based differences between patients have been discussed, they have not been shown to be definite risk factors for progression. Several authors have indicated that patients with thin corneas may be at risk for progression in primary open-angle glaucoma (21, 22). Stewart and associates recently showed that patients with central corneal thickness of ≤510 µm, although they did not require a different target IOP, more often progress with IOPs of ≥18 mmHg. This study highlighted the importance of reducing IOP in this special group of patients (6). However, the level of mean or peak IOPs that would provide safety for all patients with primary open-angle glaucoma has not yet been defined clearly (5).

The purpose of this meta-analysis was to describe progression and non-progression rates at individual mean IOP levels for patients with primary open-angle and exfoliative glaucoma.

This meta-analysis showed that there were statistical differences in the mean and peak IOPs between progressed and stable patients as calculated by the Stouffer combined test, and weighted for the sample size, from the independent studies. In addition, these results were strengthened by the multivariant regression analysis identifying the mean IOP as an independent risk variable for glaucomatous progression. This meta-analysis helps confirm the findings from the AGIS and EMGT studies that showed lower IOPs help prevent progression over 5 or more years in patients with glaucoma (2, 5). In addition, EMGT has demonstrated that for each 1 mmHg further reduction in pressure there was 11% decrease in glaucomatous progression (23).

In addition, our results demonstrated that among the specific levels of mean IOP, the percent that remained stable

showed at least three distinct regions. First, for pressures of ≥20 mmHg, a narrow majority of patients progressed. However, the percent of patients who did not progress was relatively constant over these higher levels of pressure with 48–53% remaining stable between 20 and 22 mmHg and as many as 40% at ≥23 mmHg.

Second, with decreasing pressures between 20 and 17 mmHg, there was a progressive improvement in the percentage of stable patients over time, increasing from 53 to 85%. Third, between 13 and 18 mmHg the great majority of patients remained stable. Surprisingly, the percent of patients who maintained stability was relatively consistent between 13 and 17 mmHg, ranging between 81 and 92% of patients. Why patients between 13 and 17 mmHg showed no additional gain in stability at the lower end of this range was not clear by our results.

However, a further slight improvement in the percent stable patients was observed for pressures of ≤12 mmHg (96%). Although our numbers were relatively few, our findings at IOPs of ≤12 mmHg are consistent with the AGIS study, which indicated that patients with a peak IOP never above approximately 18 mmHg, with a 12.5 mmHg mean IOP, had the best chance to remain stable (5).

Overall, this meta-analysis demonstrated the highest mean pressure allowing for at least three quarters of patients to remain stable over 5 years was 18 mmHg. Unfortunately, some patients continued to progress despite reduction of the IOP. Several factors were found that helped identify patients that might help prevent progression: higher peak IOP, older age, and exfoliative glaucoma. However, none of these factors were identified by the multivariant regression analysis as an independent risk factor although the number of patients with exfoliative glaucoma was relatively small (20%). Consequently, why some patients continue to progress despite a therapeutic decrease well into the normal range remains unknown. More research is needed to further classify patients with glaucoma to determine additional risk factors that would indicate alternative IOP levels that would help more specifically assure a stable disease course among individual patients.

As stated in Methods, the range of IOP in the exfoliative trial that prevented progression of more than two thirds of patients (17 mmHg) was within the range (16–21 mmHg) noted for the primary open-angle glaucoma studies. However, consistent with exfoliative glaucoma, the pressures were generally higher in the one included study than the primary open-angle studies included in our meta-analysis. Consequently, these patients more often progressed. The current findings are consistent with past data indicating exfoliative patients have higher pressures and are more difficult to control (24, 25).

This study suggests that maintaining an IOP well within the normal range over 5 years in patients with primary open-angle or exfoliative glaucoma helps to prevent glaucomatous progression.

This meta-analysis is limited by the retrospective design of the included studies. More long-term prospective well-controlled trials are needed to better describe progression rates at individual IOP levels. In addition, this study did not have sufficient patient numbers to evaluate the low (≤12 mmHg) or high (≥23 mmHg) extremes of pressures included in this study. More data are required to better classify progression rates at higher and lower mean pressure levels.

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