Factors Associated With Long-term Progression or Stability in Exfoliation Glaucoma

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Objective: To evaluate the effect of intraocular pressure (IOP) reduction on long-term progression or stability in patients with exfoliation glaucoma.

Design: Multicenter (Greece, Spain, Russia, and Hungary), retrospective analysis.

Methods: Medical record analysis of 167 patients with at least 5 years of follow-up, who were stable (n=85) or whose condition had progressed (n=82) after the beginning of the follow-up period.

Results: The mean±SD IOP was 18.1±2.6 mm Hg in the stable group and 20.1±4.3 mm Hg in the progressed group (P<.001). The mean±SD follow-up time was 6.1±2.3 years for the stable group and 3.4±1.7 years for the progressed group. The mean SD for each patient’s average IOP was 2.9 mm Hg for the stable group and 4.6 mm Hg for the progressed group (P<.001). Twenty-eight percent of patients who had a mean IOP of 17 mm Hg or lower, 43% of those with an IOP of 18 to 19 mm Hg, and 70% of those with an IOP of 20 mm Hg or higher progressed. Progressed patients had statistically greater optic disc damage at baseline and more medication changes and trabeculectomies during follow-up than stable patients (P<.05).

Conclusion: This study suggests that IOP reduction helps to prevent glaucoma progression in patients with exfoliation glaucoma, although it does not guarantee the prevention or worsening of the disease.

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Many investigators believe that exfoliation glaucoma is more severe than primary open-angle glaucoma (POAG). Konstas and coworkers found that the initial intraocular pressure (IOP) was higher in patients with exfoliation glaucoma than in patients with POAG. Similar findings have been noted by Tezel and Tezel, Lindblom and Thorburn, and Futa and associates, although not by Linner and associates. Further, Teus and coworkers demonstrated that higher untreated IOP levels were associated with greater visual field loss (mean deviation). Several authors have noted that over time the visual field loss and optic nerve damage in exfoliation glaucoma are more rapid and associated with a higher IOP than in POAG. Accordingly, exfoliation glaucoma is believed by many investigators to be more difficult to manage clinically, with a higher incidence of treatment failure than POAG. In a long-term study, Blika and Saunte showed that exfoliation glaucoma was controlled with a β-blocker in only 8% of patients compared with 33% of patients with POAG. Additionally, Pohjanpelti demonstrated that during approximately 10 years of follow-up, 35% of patients with exfoliation glaucoma required trabeculectomy to control their IOP compared with 18% of patients with POAG. Despite the reported incidence of increased progression compared with POAG, however, little data exist that evaluate patients with exfoliation glaucoma and the treatment end points that would help prevent glaucomatous progression and visual field loss. The purpose of this study was to retrospectively evaluate patients with exfoliation glaucoma and the treatment end points that would help prevent glaucomatous progression and visual field loss.

METHODS

We included patients who met 1 of 2 criteria: stable exfoliation glaucoma for a minimum of 5...
years or diagnosis or progression of exfoliation glaucoma during the follow-up period. Patients were chosen from consecutive medical records at the practices of the study investigators and reviewed alphabetically. Each site was asked to identify 50 consecutive patients with exfoliation glaucoma, of whom only those with glaucomatous damage were included for this analysis.

Data collection began from the patient’s initial examination. The initial IOP, however, was excluded to allow for adjustment of therapy for elevated IOP. Data were recorded from each available visit included in the follow-up period. For patients with stable glaucoma, data were collected for as long as records were available. For those with glaucoma progression, data were collected until the time the glaucoma worsened. Data were not recorded after the time of progression so that the information included in this study would reflect the ocular condition that caused the progression.

Each patient had been diagnosed by the investigator as having exfoliation glaucoma secondary to glaucomatous optic disc (neural rim thinning or notching, saucierization, thin nasal rim, or total cupping) and/or visual field changes (typical nerve fiber layer changes, including nasal step or paracentral Seidel or arcuate scotoma). Patients demonstrated typical anterior segment findings of exfoliation syndrome. Excluded from this study were patients with congenital, primary, narrow-angle, or low-tension glaucoma and patients thought to have progressive nonexfoliation glaucoma.

Data collected during the follow-up period from each visit included results of Goldmann applanation tonometry, evaluation of the ocular adnexa, and slitlamp biomicroscopy. Routine follow-up visits typically were performed every 3 to 6 months. Dilated optic disc and visual field examinations generally were completed yearly or more frequently if required. At dilated examinations, the optic disc was examined by stereoscopic techniques. The same investigator evaluated each patient during the follow-up period.

The investigator determined progression clinically. In each case, progression must have been noted in the medical record with the associated reason. Generally, the criterion for progression was an increase in thinning of the neural rim or a worsening of glaucomatous visual field loss. In patients with total glaucomatous cupping and diffusely depressed visual fields, worsened visual acuity was also used as a sign of progression. Patients without “progression” noted were assumed to be stable. One of us (W.C.S.) reviewed the suitability of the designation of each patient as stable or progressed in a masked fashion. If the medical record data seemed inconsistent with either progression or stability, the clinical findings were reviewed with the investigator to assure accuracy.

Data collection and statistical analysis between patients who were either stable or progressed were performed as follows. All data were 2-sided and unpaired. A P value of .05 was selected as determinate statistical significance. A t test was used between groups to analyze data for patient age, mean and peak IOP, the number of office visits, the number of medications changes per year, the number of medications taken at the end of the study, the study term in years, the number of laser trabeculoplasties, and the number of trabeculectomies per year. Risk factors for progression were analyzed by both a univariate analysis and a multivariate Spearman ρ correlation analysis. An F test analyzed the differences between the variance of each patient’s IOP, measured during the follow-up period.

A χ² test was used to analyze differences between groups of nonordered scores, such as left or right eye, sex, and optic disc and visual field status. A Mann-Whitney U test was used to evaluate visual acuity. If both eyes of a patient met the criteria for entrance into the study, only one eye was randomly chosen to be analyzed.

**RESULTS**

**PATIENT CHARACTERISTICS**

We included 167 patients (82 progressed and 85 stable) in this study. Baseline patient characteristics at the beginning of the follow-up period are presented in Table 1. The stable glaucoma group had a mean±SD of 13.8±7.0 visits per patient during 6.1±2.3 years, and the progressed glaucoma group had 8.5±5.1 visits during 3.4±1.7 years (Table 2).

**INTRAOCULAR PRESSURE**

The mean±SD IOP for the stable glaucoma group was 18.1±2.6 mm Hg and for the progressed glaucoma group was 20.1±4.3 mm Hg. A statistical difference existed between groups for mean IOP (P<.001). In Figure 1, the mean IOPs for each patient in both groups are shown. Several different mean IOP levels were instructive in differentiating the clinical course of patients in this study. Eleven (28%) of 40 patients with an IOP 17 mm Hg or lower had their glaucoma progress. In contrast, 29 (43%) of 67 patients with an IOP of 18 to 19 mm Hg had their glaucoma progress. Progression was more marked when IOPs were 20 mm Hg or higher (42 [70%] of 60 patients) (Figure 1).

The highest mean±SD recorded peak IOP was 24.1±5.4 mm Hg in the stable glaucoma group and 29.2±10.3 mm Hg in the progressed glaucoma group (P<.001). In addition, the mean SD of the IOP for each patient was significantly higher in the progressed (4.6 mm Hg) than the stable (2.9 mm Hg) glaucoma group (P<.001) (Table 2). Figure 2 shows the mean SD of all

<table>
<thead>
<tr>
<th>Study eye</th>
<th>Progressive Glaucoma (n = 82)</th>
<th>Stable Glaucoma (n = 85)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right eye</td>
<td>42</td>
<td>42</td>
<td>.82</td>
</tr>
<tr>
<td>Left eye</td>
<td>40</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Baseline Patient Characteristics**

- **Age, mean ± SD, y** 74.0 ± 8.3 75.0 ± 10.0 .46
- **Sex** Female 41 45 .70
- **Study eye** Right eye 42 42 .82
- **Visual acuity** 20/20-20/40 56 65
- **Visual field** No change 15 28
- **Optic disc** Mild-moderate change 15 34 .008
- **Advanced change** 65 50
- **Examination not noted** 2 1

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measured IOPs for each patient. Generally, patients whose SD was less than 3 mm Hg or lower (37% progressed glaucoma) were more stable than those whose SD was 4 mm Hg or higher (71% progressed glaucoma). Figure 3 shows the rate of progression of glaucoma during the first 5 years of follow-up.

**OTHER RISK FACTORS**

At baseline, the progressed group had significantly more advanced visual field, visual acuity, and optic disc changes by univariate analysis (Table 1). During the follow-up period, the progressed glaucoma group had significantly more office visits, laser trabeculoplasties, and trabeculectomies per year (Table 2). By multivariate analysis, a significant correlation to progression was observed with the cup-disc ratio at diagnosis, as well as the number of trabeculectomies, medication changes, and the mean IOP over time (Table 3). We examined patients with advanced optic disc damage and those with visual field changes, separately. The IOPs associated with progression or stability of the glaucoma did not change in this group compared with patients with less advanced glaucoma.

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**Table 2. Patient Follow-up Data**

<table>
<thead>
<tr>
<th></th>
<th>Progressed Glaucoma (n = 82)</th>
<th>Stable Glaucoma (n = 85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of visits per year</td>
<td>2.8 ± 1.8</td>
<td>2.2 ± 0.9</td>
<td>.009</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>20.1 ± 4.3</td>
<td>18.1 ± 2.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>4.6 ± 3.2</td>
<td>2.9 ± 1.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of medicine changes per year</td>
<td>0.4 ± 0.6</td>
<td>0.4 ± 0.2</td>
<td>.53</td>
</tr>
<tr>
<td>No. of medications at end of study</td>
<td>1.2 ± 0.7</td>
<td>1.1 ± 0.8</td>
<td>.18</td>
</tr>
<tr>
<td>Study term, y</td>
<td>3.4 ± 1.7</td>
<td>6.1 ± 2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Laser trabeculoplasties performed per year</td>
<td>0.2 ± 0.2</td>
<td>0.07 ± 0.09</td>
<td>.002</td>
</tr>
<tr>
<td>Trabeculectomies performed per year</td>
<td>0.1 ± 0.2</td>
<td>0.03 ± 0.07</td>
<td>.003</td>
</tr>
<tr>
<td>Cause for progression†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic disc and visual field</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual field</td>
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<tr>
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<td>Optic disc and visual acuity</td>
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</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.

*Unless otherwise indicated, values are presented as mean ± SD.
†This was not noted in a few patients.

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**Table 3. Multivariate Analysis for Progression With Significant Probabilities**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.31</td>
</tr>
<tr>
<td>Sex</td>
<td>.71</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>.13</td>
</tr>
<tr>
<td>Visual field</td>
<td>.80</td>
</tr>
<tr>
<td>Argon laser trabeculoplasty</td>
<td>.40</td>
</tr>
<tr>
<td>Average IOP over time</td>
<td>&lt;.001</td>
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<tr>
<td>Cup-disc ratio</td>
<td>.001</td>
</tr>
<tr>
<td>Medication changes</td>
<td>.92</td>
</tr>
<tr>
<td>Trabeculectomy</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of medication changes at end</td>
<td>.94</td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.
Controversy still exists over the proper treatment end points of patients with advanced POAG. Several historic and recent studies have demonstrated not only the benefit of IOP reduction in POAG but have indicated specific target IOPs that help prevent progressive glaucomatous damage. These reports have implied that patients with moderate or advanced glaucomatous damage usually remain stable, with a mean IOP between 15 and 18 mm Hg for 5 to 10 years.18-20 Several studies, however, have indicated a further benefit in patients with advanced glaucoma when IOPs are as low as 12 to 15 mm Hg.20,26 Higher IOPs generally led to greater incidences of progressive glaucomatous damage. For example, in 2 of these reports, patients with slightly higher mean IOPs (19-21 mm Hg) had their glaucoma progress in approximately 50% to 67% of cases, and in almost 100% of patients, progression occurred when IOPs were 22 mm Hg or higher.23,28 In addition, several studies have noted that the extent and rate of glaucomatous damage are worse with higher peak IOPs.23,28-32 However, the level of mean or peak IOPs that would provide safety for all patients has not yet been defined clearly.26

More data are needed to establish treatment end points that will help preserve vision in patients with exfoliation glaucoma. Such information is especially important for these patients for 2 reasons. First, exfoliation glaucoma is a more severe form of glaucoma, more often associated with vision loss than POAG. Second, although not as common as POAG, exfoliation glaucoma is probably the most common identifiable entity that leads to glaucoma.34 Further, in some populations (eg, Baltic and Mediterranean), its incidence may reach a higher percentage of the population than the primary form of the disease.34

We evaluated the long-term follow-up in patients with exfoliation glaucoma to determine treatment levels that would help prevent progression. Our results indicated that patients with an IOP of 17 mm Hg or lower were most likely to remain stable during 5 to 10 years of follow-up. Twenty-eight percent of these patients’ glaucoma progressed during this time. However, some patients with mean IOPs of 13 mm Hg still had their glaucoma progress during the follow-up period. Two patients with an IOP of 12 mm Hg or lower remain stable; however, this was too few patients to determine if this was a safe level or not. Patients with an IOP of 18 to 19 mm Hg demonstrated a 43% chance of progression of their glaucoma during the follow-up period. In contrast, patients with a mean IOP of 20 mm Hg or higher had a 70% incidence of progression. In addition, progressed glaucoma patients had a statistically greater peak IOP and variation of IOP over time.

The findings in this study mirror those found previously in patients with POAG. These studies showed that IOPs of 17 to 18 mm Hg or lower were required to help prevent progression of their glaucoma for 5 to 10 years. They, too, noted that elevated peak IOPs more often lead to progression.

The patient characteristic at baseline that was associated with progression by multivariate analysis was more advanced optic disc damage. However, the IOP levels required to control glaucoma progression in patients with advanced disc and field damage were not different from those required for patients with less advanced disease. This finding was consistent with a recent study performed in a similar fashion with POAG patients.23 Other characteristics of patients whose glaucoma progressed during the follow-up period included a greater number of medication changes and trabeculectomies per year. These findings may indicate that physicians had a more difficult time controlling the progressed group, allowing for higher IOPs and a greater tendency for glaucomatous damage.

Unfortunately, some patients with reduced IOP did continue to have their glaucoma progress. It is not clear from the results of this study why IOP reduction does not completely stabilize vision. It could be that other factors exist, apart from the IOP, in some patients with exfoliation glaucoma that cause them to be more susceptible to progression. Determining such factors in the future might lead to new treatments to better stabilize IOPs in patients with this disease.

Our findings suggest that IOP reduction helps to prevent glaucoma progression in patients with exfoliation glaucoma, although it does not guarantee the prevention or worsening of the disease. This study did not evaluate patients in a prospective manner. Such research is needed to confirm these findings as well as to identify specific risk factors that would help further subclassify patients with exfoliation glaucoma and potentially lead to new IOP treatment parameters for these groups to help stabilize this disease. In addition, this study did not evaluate all populations with this disease. Intraocular pressure requirements may differ in other genetically distinct populations with exfoliation glaucoma.

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REFERENCES

9. Linnér E, Schwartz B, Araujo D. Optic disc pallor and visual field defect in exfo-


