A 10-Year Follow-up to Determine the Effect of YAG Laser Iridotomy on the Natural History of Pigment Dispersion Syndrome
A Randomized Clinical Trial

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**IMPORTANCE** Prospective long-term analyses of the role of drug-induced mydriasis and laser peripheral iridotomy (LPI) are needed to identify and manage the eyes of patients with pigment dispersion syndrome (PDS) at risk for progressing to ocular hypertension.

**OBJECTIVE** To assess the 10-year incidence of increased intraocular pressure (IOP) in the 2 eyes of patients with PDS, with 1 eye that underwent LPI and the other that did not.

**DESIGN, SETTING, AND PARTICIPANTS** In a randomized clinical trial in the glaucoma research unit at the University Hospital of Parma, Italy, 72 patients with PDS underwent phenylephrine testing. Of these 72 patients, 29 (58 eyes) tested positive for succeeding IOP elevation, and 43 (59 eyes) tested negative. For the 29 high-risk patients (all in both eyes), one eye was randomly assigned to LPI, and the fellow eye was left untreated. For the 43 low-risk patients, the affected eyes were left untreated.

**MAIN OUTCOMES AND MEASURES** An IOP elevation of 5 mm Hg or higher vs baseline (daily phasing) was considered to be a significant increase (ie, an event).

**RESULTS** In the high-risk group, 3 of 21 eyes that underwent LPI (14.3%) and 13 of 21 untreated eyes (61.9%) showed an increase in IOP of 5 mm Hg or higher during the follow-up period; 4 of 35 low-risk eyes (11.4%) showed a similar increase. Event-free mean (SD) time was 7.99 (0.43) years for high-risk treated eyes, 3.89 (0.68) years for high-risk untreated eyes, and 7.16 (0.23) years for low-risk eyes. The log-rank test showed the following: \( P < .001 \) for treated high-risk eyes vs untreated high-risk eyes, \( P = .74 \) for treated high-risk eyes vs low-risk eyes, \( P < .001 \) for untreated high-risk eyes vs low-risk eyes.

**CONCLUSIONS AND RELEVANCE** At the end of the 10-year follow-up, (1) approximately one-third of the whole PDS patient population showed an IOP increase of 5 mm Hg or higher in at least 1 eye; (2) phenylephrine testing identified eyes at high risk for developing IOP elevation; and (3) LPI, when performed on high-risk eyes, reduced the rate of IOP elevation to the same level as the low-risk eyes.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01053416
Eyes affected by pigment dispersion syndrome (PDS) typically show midperipheral, slitlike iris pigment epithelial defects, deposition of pigment granules on the anterior segment structures of the eye, and a “floppy” iris root, often (but not always) assuming a concave configuration. Liberation of pigment occurs after repeated contact of the posterior iris surface of a concave iris with the lens zonules and anterior lens capsule. In the long run, the overload of pigment affects the trabecular meshwork, leading to a progressive increase in intraocular pressure (IOP), followed by the occurrence of glaucomatous damage to the optic nerve (pigmentary glaucoma [PG]).

The backward movement of the iris root (the so-called reverse pupillary block) is an accepted mechanism for pigment dispersion. This seems to be triggered by blinking, accommodation, and pupillary dilation, and it is more likely to occur in eyes showing a concave iris root. Campbell hypothesized that an iridotomy could be beneficial in eyes showing a reverse pupillary block, slowing the rate of progression from PDS to PG. A flattening of the concave iris root, with an eventual decreased iridolenticular contact, was in fact described after Nd:YAG laser peripheral iridotomy (LPI) was performed on eyes with PDS or PG.

The aim of our study was to determine the 10-year benefit of Nd:YAG LPI in reducing the incidence of significant IOP elevation in PDS eyes considered at high risk for progression to PG. A 2-year interim analysis was published previously.

Methods

Our study was conducted in the glaucoma research unit at the University Hospital of Parma (Italy). The protocol was approved by the ethics committee of the hospital, and written informed consent was obtained according to the tenets of the Declaration of Helsinki. Participants were not financially compensated.

Background

From 1990 to 1991, 1154 workers in the Parma area were screened for fitness for long-term use of a video monitor; 86 were referred to the glaucoma research unit for suspected PDS. The diagnosis was confirmed for 72 participants (117 eyes), based on the following criteria:

- Deposition of pigment on the corneal endothelium (Krukenberg spindle);
- At least 1 midperipheral, slitlike iris defect detected by transillumination with a slitlamp;
- Deposition of brownish pigment on the angle structures for 270° or more;
- An IOP of less than 18 mm Hg;
- Absence of pseudoxfoliative material on the anterior lens capsule (full mydriasis) and on the pupillary border; and
- Absence of glaucomatous visual field defect.

Patient Selection and Randomization for Treatment

A phenylephrine provocative test was performed on all patients with PDS. The test was performed by instilling 1 drop of phenylephrine hydrochloride, 10%, 3 times every 5 minutes. The liberation of pigment was graded with a slitlamp according to the modification of the Mitsui and Takagi scale by Epstein et al. The test result was positive if at least 10 particles were detected in a single light beam (ie, the lowest grade on a 1-4 scale in Epstein et al, corresponding to grade 3 on a 0-6 scale in Mitsui and Takagi). For safety reasons, IOP was checked 60 and 120 minutes after instillation of the mydriatic agent. Patients who had a positive phenylephrine test result were considered to be at high risk for succeeding IOP decompensation. Patients who had a negative phenylephrine test result were then considered to be at low risk. No patient had one eye that was at high risk and the other that was at low risk.

Gonioscopy was performed to evaluate the iris root in each eye. In brief, gonioscopy was performed by the same investigator (S.A.G.), and the iris root was evaluated in both basal conditions and by accommodation. Accommodation was elicited by asking the patient to fixate with the fellow eye on a nearby target (ie, the number on the slitlamp enlargement rotary). The iris root was qualified as “concave” when assuming a concave configuration in either condition (basal or by accommodation). The iris root configuration was confirmed by ultrasound biomicroscopy analysis, which was performed during follow-up, when this technology became available in our clinic (since 2002).

High-risk patients were asked to participate in the “active” part of the study, a randomized clinical trial of the efficacy of laser iridotomy. When both eyes of a high-risk patient were eligible for treatment, one eye was randomly assigned (using a biased coin method on a computerized system) to undergo Nd:YAG LPI, and the fellow eye was left untreated as a control. Nd:YAG LPI was performed according to a procedure described previously. Low-risk patients were left untreated as a control, contributing further to the “natural history” part of the study. To avoid potential statistical bias (in particular, the possible correlation between a person’s right and left eyes), for low-risk patients with bilateral involvement, only one eye (the right eye) was arbitrarily considered for our study. For high-risk patients, the application of a pure mechanical treatment such as Nd:YAG LPI for one eye was unable to influence the clinical course of the fellow eye or, at worst, was responsible for an underestimation of p values and confidence intervals. Once qualified for follow-up, patients were regularly checked every 6 months (±1 month).

Examination Procedure

The IOP, best-corrected visual acuity, lens transparency, optic nerve head, and visual field were assessed at baseline and at every follow-up visit. Examination procedures have been partly described in a previous study. A more detailed description is hereby reported.

The main outcome measure was IOP. Daily phasing (6 readings, from 8:00 AM to 6:00 PM) was performed at every planned follow-up visit. Intraocular pressure was measured by 2 “masked” investigators (one rotating the dial and the other reading the value on the dial). Masking was achieved by performing tonometry before the slitlamp examination. Two readings were performed. In the case of a difference of more than 2 mm Hg between the readings, a third reading was obtained, and the 2 closest values were averaged. Having 6 indepen-
dent values for each daily phasing, we considered the IOP representative of that phasing of the average of the 2 highest values. Calibration of the tonometer was performed routinely, according to the standardized operating procedure of the Clinical Trial Site of the European Vision Institute (http://www.europeanvisioninstitute.org/news/evi-the-news-details/article/european-vision-institute-clinical-trials-sites-of-excellence.html).

Best-corrected visual acuity was a safety outcome measure. Patients were asked to read the Early Treatment Diabetic Retinopathy chart, placed at a distance of 4 m, until no more letters could be identified correctly. The letters properly identified were then counted, and the corresponding logMAR was recorded.

Lens transparency was a safety outcome measure. The state of the lens was assessed in full mydriasis with a slit lamp by 2 masked investigators (S.A.G. and N.U.) referring to the Lens Opacity Classification System II.

The optic nerve head was a safety outcome measure. The optic nerve head was observed regularly with a slit lamp in full mydriasis, in the framework of a complete examination of the posterior pole and the peripheral retina.

The visual field was a safety outcome. A visual field examination was performed using computer-assisted static perimetry. The Octopus program GI (Interzeag) was used for the first 3 years of follow-up, and then a Humphrey 24-2 SITA (Swedish Interactive Thresholding Algorithm) standard program (Carl Zeiss Meditec) was used for the remainder of follow-ups.

### Statistical Methods and Data Analysis

As reported in the interim analysis, the occurrence of an increase in IOP of 5 mm Hg or higher with respect to the baseline visit was adopted for the definition of a significant increase in IOP, and it was considered to be the “event” that the study was tailored to detect. This definition is consistent with that suggested by Epstein et al and for properly defining “pigmentary glaucoma suspects” (ie, patients with PDS who have an IOP of 22-23 mm Hg).

The trial was designed to detect differences in the event (1) between high-risk eyes that had undergone Nd:YAG LPI and untreated high-risk control eyes (the interventional arm), and (2) between low-risk control eyes and untreated high-risk control eyes (the observational arm). The sample size was adequate to allow detection of a 45% difference in the event rate either between treated and untreated high-risk eyes or between high- and low-risk eyes (type I error: α = .05, 95% power). Between groups, the mean value differences in normally distributed parameters were analyzed using the t test. Proportions were compared using the Fisher exact test. Statistical significance was set at P < .01. For the follow-up analysis, Kaplan-Meier plots were prepared for each group of patients (ie, patients with treated and untreated high-risk eyes and patients with low-risk eyes) and compared using the log-rank test (XLSTAT 2012.5.02 software).

### Results

In total, 29 patients with PDS had a positive phenylephrine test result (ie, 58 high-risk eyes, all bilateral), and 43 patients with PDS had a negative phenylephrine test result (ie, 16 low-risk patients with PDS in both eyes and 27 low-risk patients with PDS in 1 eye). Of the 59 low-risk eyes, only 43 (1 eye for each patient) were considered for the study. The demographics of the high- and low-risk groups are detailed in the Table. No significant difference was found for any parameter. All 58 high-risk eyes were assessed and had a concave iris root. Four of the 43 low-risk eyes had a concave iris root.

Two of the 58 high-risk eyes and 1 of the 59 low-risk eyes showed an increase in IOP of higher than 2 mm Hg 1 hour after the phenylephrine test. This was consistent with what was stated in a previous study.

Nd:YAG LPI was performed on 1 eye (randomly assigned) of each of the 26 high-risk patients who agreed to have the procedure (3 of the 29 patients refused). Of these 26 patients, only 21 (42 eyes) were followed up (because 4 requested immediate laser treatment in the fellow eye and 1 died before the baseline visit). In the low-risk group, 8 patients dropped out of the study. Thus, 35 low-risk patients (35 eyes) were qualified for follow-up (Figure 1). Sixteen high-risk patients (32 eyes) and 30 low-risk patients (30 eyes) completed the 10-year follow-up. Ten patients (5 high-risk patients and 5 low-risk patients) were lost to follow-up. None of these patients lost to follow-up had shown an IOP elevation of 5 mm Hg or higher before they dropped out of the study.

In the high-risk group, 3 of 21 eyes that had undergone Nd:YAG LPI (14.3%) and 13 of 21 untreated eyes (61.9%) had shown an IOP elevation of 5 mm Hg or higher. The 3 patients who had undergone Nd:YAG LPI and had shown an IOP elevation of 5 mm Hg or higher also experienced a conversion from

### Table. Demographic Characteristics of the 2 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-Risk Group (n = 21)</th>
<th>Low-Risk Group (n = 35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, No. (%)</td>
<td>14 (67)</td>
<td>23 (66)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>34 (19-60)</td>
<td>31 (21-52)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Refraction (spherical equivalent), D</td>
<td>−3.1 (1.5)</td>
<td>−2.5 (2.5)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>IOP, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated eyes</td>
<td>14.3 (2.3)</td>
<td>15.0 (1.9)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Untreated eyes</td>
<td>13.9 (2.2)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>BCVA, mean (SD), logMAR</td>
<td>−0.06 (0.08)</td>
<td>−0.04 (0.10)</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Snellen equivalent</td>
<td>20/20 (20/25)</td>
<td>20/20 (20/25)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; D, diopters; IOP, intraocular pressure; NA, not applicable.

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PDS to PG in the untreated fellow eye. In the low-risk group, 4 of 35 eyes (one with a concave iris root) had shown an IOP elevation of 5 mm Hg or higher (11.4%). The overall 10-year event rate for eyes that had not undergone Nd:YAG LPI (ie, untreated high- and low-risk eyes) was 30.4%. All these converting eyes showed an iridocorneal angle in near vision of greater than 53° when tested by ultrasound biomicroscopy during follow-up.13 Statistical analysis showed that the mean (SD) “survival” time (ie, the mean time during which the eyes were event-free) was 7.99 (0.43) years for the treated high-risk eyes, 3.89 (0.68) years for the untreated high-risk eyes, and 7.16 (0.23) years for the low-risk eyes. The log-rank test showed the following: \( P < .001 \) for treated high-risk eyes vs untreated high-risk eyes, \( P = .74 \) for treated high-risk eyes vs low-risk eyes, and \( P < .001 \) for untreated high-risk eyes vs low-risk eyes (Figure 2).

No significant difference in age was found between any patients who experienced an event (mean [SD] age, 29 [7] years) and any event-free patients (33 [10] years) (\( P = .15 \)). However, when the age analysis was performed within the 2 groups (ie, the high- and low-risk groups), we found that, in the high-risk group, the 13 patients who experienced an event were significantly younger than the 16 event-free patients (27 [6] years vs 41 [12] years; \( P = .002 \)); in the low-risk group, the mean age was statistically comparable between patients who experienced an event and event-free patients.

Two eyes included in the treated high-risk group and 2 eyes included in the untreated high-risk group became worse (by at least 1 step in the Lens Opacity Classification System II for cataracts). On occurrence of the event, the 3 eyes in the treated high-risk group underwent argon laser trabeculoplasty; in 2 of these eyes, latanoprost, 0.005%, every day was also prescribed to reach the estimated target IOP. The 13 eyes that had shown an IOP elevation of 5 mm Hg or higher (ie, the event) in the untreated high-risk group were treated as follows: Nd:YAG LPI (100% of eyes), argon laser trabeculoplasty (6 eyes), and topical hypotensive drugs (10 eyes). The 4 low-risk eyes that had shown an IOP elevation of 5 mm Hg or higher were treated as follows: Nd:YAG LPI (the 1 eye showing a concave iris root), argon laser trabeculoplasty (4 eyes), and additional topical hypotensive drugs (1 eye). No eye showed visual field progression (defined as a point being flagged at \( P < .05 \) in the corrected pattern standard deviation or having glaucoma hemifield test results outside normal limits) during follow-up.

### Discussion

The data collected from the study cohorts during the 10-year follow-up provide the following evidence: (1) approximately...
one-third of all patients with PDS showed an increase in IOP of 5 mm Hg or higher in at least 1 eye; (2) dispersion of pigment after drug-induced mydriasis could support the identification of those PDS eyes at high risk for elevated IOP; and (3) Nd:YAG LPI, when performed on high-risk eyes, reduced the rate of IOP elevation to the same level as the low-risk eyes. If we assume that the development of ocular hypertension in PDS eyes is the first step in the continuum to PG, our data can be interpreted within the framework of the possible prevention of, or delay in, the conversion from PDS to PG.

The actual rate of conversion from PDS to PG is still a matter of debate. Migliazzo et al described 35% of patients with PDS and ocular hypertension developing disc and field changes over a mean follow-up of 17.3 years. Farrar et al, while following a group of patients affected by PDS or PG, showed a 50% conversion rate over a mean follow-up of 4.3 years. In a retrospective community-based study, the probability of converting from PDS to PG was 10% at 5 years and 15% at 15 years. More recently, Scott et al reported that 17% of eyes with PDS and a mean basal IOP of 23.7 mm Hg were started on medical treatment during a 3-year follow-up. Because of the heterogeneity of the definitions of “conversion” that have been adopted to date, it is almost impossible to compare our results with the data already mentioned. However, a tentative summary is shown in Figure 3.

Determining which eye affected by PDS will eventually develop PG can be difficult. “Active” pigment dispersion (ie, the detection over time of an increased amount of pigment deposition on anterior segment structures) seems to be a major risk factor for conversion. Interestingly, Küchle and coworkers observed melanin granules in the anterior chamber of patients with PDS, the density being increased by pupillary dilatation. However, as suggested by Schenker et al, “a pupillary movement, and the induced mechanical abrasion of pigment epithelium, while necessary to induce liberation of pigment, are not always sufficient to do so.” Concurrent abnormalities of the iris, as well as comorbidities and genetic factors, must play a role in facilitating the loss of pigment from the posterior iris surface. In our study, 58 of 117 PDS eyes had a positive phenylephrine test result. When left untreated, more than 60% of these eyes showed an increase in IOP of 5 mm Hg or higher during the 10-year follow-up. Conversely, around 10% of those eyes that had a negative phenylephrine test result also had the same increase in IOP. We can then assume that the test was able to separate those eyes showing a relatively unstable iris pigment epithelium, leading to “active pigment dispersion” and to the eventual development of ocular hypertension. Otherwise, the positive predictive value of such a test is not absolute, considering that 4 of 25 low-risk eyes showed an increase in IOP of 5 mm Hg or higher and that 8 of 21 untreated high-risk eyes did not develop ocular hypertension over the course of the whole follow-up period.

For the high-risk group, at the end of our follow-up, patients who showed an increase in IOP of 5 mm Hg or higher were significantly younger than event-free patients. This result confirms our 2-year ad interim analysis, which showed that the difference in IOP between the treated eyes and the untreated fellow eyes correlated inversely with age. Owing to the small number of patients involved, however, this result is too underpowered for any possible further inference.

While studying the occurrence of pigment liberation in PDS, Küchle et al found that Nd:YAG LPI resulted in a significant decrease in aqueous melanin granules in eyes with PDS in both basal conditions and on dilatation. A lower amount of pigment liberation can eventually lead to a decreased risk of impairment of a vital and still-functioning trabecular meshwork with a lower incidence of ocular hypertension. Interestingly, iridotomy did not offer any benefit when performed on PDS eyes showing an already increased IOP or on eyes affected by PG. This is not surprising; as already stated, Nd:YAG LPI is only expected to “prevent” pigment liberation in the anterior chamber. If the trabecular meshwork is still functioning, Nd:YAG LPI will stop pigment from damaging it, thereby “preventing” ocular hypertension. If ocular hypertension has already occurred, the trabecular meshwork can be assumed to already be damaged. Thus, Nd:YAG LPI will be less effective or not effective with respect to IOP in the long term.
In addition, Nd:YAG LPI, by restoring the normal iris configuration, is expected to be effective in PDS eyes showing a concave iris root. This was the case in no more than half of the patient population in the study by Scott et al.17 Meanwhile, no data on iris root configuration were reported in a retrospective study on PG.7 In the present study, PDS eyes showing both a peak IOP of less than 18 mm Hg and a concave iris root were randomly assigned to Nd:YAG LPI. These stringent criteria may explain the positive outcome of this trial.

Conclusions

In conclusion, our 10-year follow-up study suggests that drug-induced mydriasis can help in identifying PDS eyes at risk for progressing to ocular hypertension. Nd:YAG LPI, when performed at the appropriate time and on high-risk eyes showing a concave iris root, can be protective over the long term.