Short-Term Effects of Latanoprost on Anterior Chamber Depth in Patients with Glaucoma or Ocular Hypertension

Consuelo Gutiérrez-Ortiz,1 Miguel A. Teus,1,2,3 and Gema Bolivar1

PURPOSE. Prostaglandin F2α analogues, such as latanoprost, may cause a decrease in the extracellular matrices, such as collagen, and changes in fibrillin-1; both are components of the ciliary zonules. However, the mechanical effect of these changes on the dynamics of the ciliary zonules is unknown. This study was conducted to evaluate the effect of latanoprost 0.005% on anterior chamber depth (ACD), best corrected visual acuity (BCVA), lens thickness, and anterior chamber dynamics in patients with glaucoma or ocular hypertension.

METHODS. This was a prospective, nonrandomized, autocomparative trial that included 40 patients (40 eyes) with glaucoma or ocular hypertension. ACD was measured with ultrasonography before and after 1 month of treatment with latanoprost. In addition, ACD was measured before and 1 hour after instillation of pilocarpine 2% at baseline and 1 month after treatment with latanoprost. To assess the reproducibility of the ultrasonic measurements, a control group of 20 patients (20 eyes) who did not receive latanoprost was also analyzed.

RESULTS. The mean ACD before treatment with latanoprost and before the instillation of pilocarpine was 3.14 ± 0.46 mm (SD) and after the instillation of pilocarpine, 3.04 ± 0.46 mm (SD). After 1 month of treatment with latanoprost, ACD was 2.98 ± 0.44 mm (SD) before instillation of pilocarpine and 2.91 ± 0.49 mm (SD) after instillation of pilocarpine. P ≤ 0.05 was reached for all comparisons.

CONCLUSIONS. These findings suggest that latanoprost decreases ACD in patients with glaucoma or ocular hypertension after 1 month of treatment. (Invest Ophthalmol Vis Sci. 2006;47: 4856 – 4859) DOI:10.1167/iovs.06-0011

Latanoprost, a prostaglandin F2α analogue, is an effective ocular antihypertensive agent for the management of intraocular pressure (IOP). The drug is probably one of the most potent IOP-lowering medications available today and has become one of the most effective antiglaucoma agents. Induction of matrix metalloproteinase (MMP)-1, -3, and -9 expression is believed to be the mechanism by which latanoprost lowers IOP.1-3

Latanoprost 0.005% has been shown to reduce IOP by 25% to 35% with a single daily dose4,5 by increasing the aqueous outflow through the uveoscleral pathway.6-7 In addition, prostaglandins seem to modify both the physiology and the structure of the uveoscleral pathway. In fact, some studies have shown that prostaglandins induce extracellular matrix remodeling by widening the intermuscular spaces along the longitudinal ciliary muscle bundles, fragmenting collagen types I and III,6 reducing the density and the branching of type IV collagen and laminin, and reducing the density of type III collagen.7

It is well known that collagen IV is also present in the human zonules.10 In addition, fibrillin-1 is a major component of the ciliary zonules (Mayne R et al. IOVS 1997;58:ARVO Abstract 1399) and the zonular microfibrils are fragmented by the metalloproteinases.11 Thus, it makes sense that the structure and perhaps the dynamics of the ciliary zonules and the ciliary muscle could be modified by treatment with prostaglandin analogues.

Anterior chamber depth (ACD) decreases when the ciliary muscles contract either because of the physiological stimulus of accommodation or because of the instillation of topical pilocarpine.12 Therefore, we hypothesized that the biological changes induced by latanoprost on the ciliary zonules may affect mechanical behavior and therefore affect ACD after treatment with this drug. The objective of the present study was to determine whether there are modifications in ACD after treatment with latanoprost and the possible changes in the dynamics of ACD induced by pilocarpine in these eyes, because, to the best of our knowledge, there has not been a prospective study addressing this subject.

MATERIALS AND METHODS

In this prospective, nonrandomized, autocomparative trial, we evaluated consecutive patients who had received a diagnosis of primary open-angle glaucoma (POAG) or ocular hypertension (OHT) between January and October 2005 in the Glaucome Unit of the Hospital Universitario Príncipe de Asturias, Madrid, Spain.

Glaucoma was defined as the combination of a typical glaucomatous optic neuropathy (GON) and the corresponding visual field defect. The visual fields were analyzed (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Oberkochen, Germany), using the white-on-white 24-2 SITA standard strategy. The level of IOP was not used as a criterion for glaucoma diagnosis; therefore, in some patients the IOP level was within normal limits.

OHT was defined as an IOP exceeding 24 mm Hg on at least two different measurements performed on two different days, without any sign of GON and normal findings in a white-on-white 24-2 SITA standard visual field test.

Exclusion criteria were the presence of any other ophthalmic disease, a history of ocular trauma, pseudoexfoliation syndrome, any sign of zonular weakness, or any corneal disorder. Only patients with newly diagnosed glaucoma or ocular hypertension were included, to ensure that no eye had been treated with antiglaucoma drugs before the patient entered the study. When both eyes of the same patient fulfilled the inclusion criteria, only the right eye was included in the study.

An experienced observer masked to the treatment performed all measurements. ACD and lens thickness were measured with a contact, A-mode ultrasound device (OcuScan Ophthalmic Ultrasound System; Investigative Ophthalmology & Visual Science, November 2006, Vol. 47, No. 11 Copyright © Association for Research in Vision and Ophthalmology

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Submitted for publication January 6, 2006; revised April 23 and June 25, 2006; accepted September 6, 2006.

Disclosure: C. Gutiérrez-Ortiz, None; M.A. Teus, None; G. Bolivar, None.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked ‘advertisement’ in accordance with 18 U.S.C. §1734 solely to indicate this fact.

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Alcon. Fort Worth, TX) before (baseline) and after 1 month of treatment with latanoprost 0.005% (Xalatan; Pfizer Inc., New York, NY). In addition, the ACD and lens thickness were evaluated 1 hour after the topical instillation of pilocarpine 2% (Colircusi Pilocarpina 2%; Alcon, El Masnou, Spain) before and after 1 month of latanoprost therapy. The ultrasound device was set to the automatic mode, so that 10 measurements of both parameters studied were obtained, and all 10 measurements were used to calculate the mean ACD and the mean lens thickness in each examination. ACD was defined as the distance between the posterior corneal surface and the anterior lens surface echoes. The lens thickness was defined as the distance between the central anterior and central posterior lens capsule echoes.

During the measurement, the patient was asked to fixate on a Landolt C chart with the study eye; the contralateral eye was occluded to avoid convergence movements during the measurement. The measurements were performed with the target positioned 6 m away. Pilocarpine 2% was used because this drug induces maximum ciliary muscle contraction 1 hour after instillation.12

IOP was measured first, and then the ultrasonic measurements were performed in the morning, between 10 AM and 12 PM, with at least 1 hour between the measurements.

The study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional review board of our hospital. The procedure was fully explained to the patients, as were other therapeutic options. All patients provided informed consent.

At baseline, the ophthalmic variables recorded included patient age, gender, previous ocular treatments, type of glaucoma, IOP (measured by Goldmann applanation tonometry) best-corrected visual acuity (BCVA), ACD, lens thickness, and ACD and lens thickness 1 hour after the instillation of pilocarpine 2%.

All visual acuity (VA) tests were performed with the best spectacle correction of both sphere and cylinder. The best corrected distance VA (BCDVA) was assessed with the Early Diabetic Treatment Retinopathy Study reading chart 1 (Precise Vision, La Salle, IL) at a fixed distance of 4 m. One month after treatment with latanoprost 0.005%, the IOP (measured by Goldmann tonometry), VA (with the same optical correction as in the baseline examination), ACD, and lens thickness before and 1 hour after the instillation of pilocarpine 2% and the possible side effects of the therapy were recorded.

To assess the reproducibility of the A-scan measurements, a control group was established that comprised patients with newly diagnosed POAG or OHT who had not been treated with any antiglaucoma therapy. Measurements of ACD and the lens thickness before and after instillation of pilocarpine 2% were performed 1 week apart in the same fashion as in the study group (10 measurements per eye) and by the same examiner.

### Table 1. Demographic Data and Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 40)</th>
<th>Group 2 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (40)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (60)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Glaucoma type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic open angle</td>
<td>26 (65)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>14 (35)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Medications used before study</td>
<td>0 (100)</td>
<td>0 (100)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65.9 ± 8.3</td>
<td>57.1 ± 14.14</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>25.58 ± 4.43</td>
<td>22.25 ± 2.53</td>
</tr>
<tr>
<td>BCVA</td>
<td>20/32 ± 0.31</td>
<td>20/20 ± 0.22</td>
</tr>
</tbody>
</table>

All subjects were white. All had used medications before the study.

### Statistical Analysis

Statistical analysis was performed with the two-tailed paired Student’s t-test and Pearson’s correlation coefficient, when appropriate. Continuous variables data are expressed as the mean ± SD unless otherwise specified. All analyses were performed with commercially available software (SPSS 10.0 for Windows; SPSS Inc., Chicago, IL). P ≤ 0.05 was considered statistically significant.

### RESULTS

A total of 60 eyes of 60 patients were included (group 1, 40 study eyes; group 2, 20 control eyes). Table 1 lists the patients’ demographic data.

In group 1, the mean IOP before therapy (±SD) was 25.58 ± 4.43 mm Hg (range, 19–38), which decreased to 16.70 ± 6.56 mm Hg after 1 month of treatment with latanoprost (P = 0.000). The mean IOP reduction was 34.71%. The baseline mean BCDVA was 20/32 ± 0.31 (range, 20/63–20/20), and after treatment it was 20/32 ± 0.28 (range, 20/62–20/20; P = 0.66).

In group 1 at the baseline examination and before the instillation of pilocarpine 2%, the mean ACD was 3.14 ± 0.46 mm, whereas 1 month after latanoprost treatment it was 2.98 ± 0.44 mm (P = 0.05). At the baseline examination and 1 hour after the instillation of 2% pilocarpine, the mean ACD was 3.04 ± 0.46 mm and after 1 month of treatment with latanoprost, it was 2.91 ± 0.49 mm (P=0.024; Table 2).

In group 1, at the baseline examination and before the instillation of pilocarpine 2%, the mean lens thickness was 4.50 ± 0.5 mm and after 1 month of treatment with latanoprost, it was 4.45 ± 0.5 mm (P = 0.6). At the baseline examination and 1 hour after the instillation of pilocarpine 2%, the mean lens thickness was 4.50 ± 0.5 mm and it was 4.6 ± 0.64 mm after 1 month of latanoprost treatment (P = 0.5; Table 2).

The side effects associated with latanoprost were mild. The most common was conjunctival hyperemia in 10 patients (25%).

In group 2, the mean IOP was 22.25 ± 2.53 mm Hg (range, 18–27) at the first visit, and it was 22.56 ± 3 mm Hg (range, 17–28) at the second visit 1 week later (P = 0.7).

In group 2 during the first examination the mean ACD was 2.99 ± 0.38 mm and during the second examination, the mean ACD was 2.99 ± 0.39 mm (P = 0.94). At the first examination
and 1 hour after pilocarpine 2% instillation, the mean ACD was 2.88 ± 0.34 mm. During the second examination and after instillation of pilocarpine 2%, the mean ACD was 2.89 ± 0.38 mm (P = 0.84; Table 3).

In the same control group, before instillation of pilocarpine 2% the mean lens thickness was 4.5 ± 0.42 mm during the first examination and 4.5 ± 0.46 mm during the second examination (P = 0.9). After instillation of pilocarpine 2% during the first examination, the mean lens thickness was 4.56 ± 0.43 mm and during the second examination the mean lens thickness after pilocarpine instillation was 4.56 ± 0.39 mm (P = 0.9; Table 3).

No significant correlation was found between the magnitude of the latanoprost-induced IOP decrease and the latanoprost-induced ACD decrease in group 1 (r = −0.16) (P = 0.48). In the same way, no other baseline factor, such as the severity of the visual field defect, age, or gender seemed to influence changes in ACD induced by latanoprost.

**DISCUSSION**

Our study showed that topical therapy with latanoprost decreases ACD in patients with glaucoma or OHT without affecting the VA or lens thickness. We also found that the effect of topical pilocarpine on ACD after treatment with latanoprost is the same as before the therapy was started.

The ultrasound device used in this study has been shown to give consistent results with good reproducibility. Furthermore, there was no significant difference between ACD and lens thickness measurements on two repeated examinations in the same control eyes on two separate days—in fact, the results were virtually the same. Based on these results, we believe that the differences found in the study group reflect real changes in the parameters analyzed.

Previous studies have identified biological changes induced by prostaglandins (Mayne R et al. *IOVS* 1997;38:ARVO Abstract 1399) on the ciliary zonular fibers. Our results are consistent with findings in those studies and could reflect the mechanical effect of these biochemical changes.

Latanoprost may decrease ACD by three main mechanisms: thickening of the lens, zonular relaxation, or ciliary muscle contraction.

First, we found that the shallowing of the AC induced by this drug is not the result of a change in the lens shape, because the difference in lens thickness was not altered significantly by latanoprost.

However, should latanoprost induce ciliary muscle contraction, then the effect of pilocarpine on ACD before and after 1 month of treatment with latanoprost would probably have been different, and according to our results, the decrease in ACD induced by pilocarpine remained unchanged after latanoprost therapy.

In addition, some studies have shown that latanoprost does not cause significant contraction of the ciliary muscles. Yamaji et al. investigated the effects of several prostaglandins and latanoprost-free acid on the electrically evoked contractile response of isolated ciliary muscles in rhesus monkeys and showed that latanoprost-free acid did not significantly change the response amplitude of this muscle. Furthermore, Yoshitomi et al. reported that latanoprost did not affect the contraction evoked by field stimulation, which indicates that this drug has no presynaptic effect.

Another mechanism by which latanoprost could modify ACD is by relaxing the ciliary zonules. Some components of the ciliary zonules such as fibrillin 1 and collagen IV can be modified by prostaglandins and metalloproteinases. The glycoprotein fibrillin is the principal component of the ciliary zonule and has an important role in the strength and elasticity of ocular connective tissues. The microfibrils of the ciliary zonules are almost exclusively composed of fibrillin-1 (Mayne R et al. *IOVS* 1997;38:ARVO Abstract 1399), which may provide force-bearing structural support to tissues. One study showed that members of the MMP family of enzymes can degrade recombinant fibrillin-1 molecules and disrupt fibrillin-

<table>
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<tr>
<th>Parameter</th>
<th>Baseline First Examination</th>
<th>Baseline Second Examination</th>
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<tbody>
<tr>
<td>Anterior chamber depth (mm)</td>
<td>Before pilocarpine 2.99 ± 0.38</td>
<td>Before pilocarpine 2.99 ± 0.39</td>
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<td></td>
<td>After pilocarpine 2.88 ± 0.34</td>
<td>After pilocarpine 2.89 ± 0.38</td>
</tr>
<tr>
<td>Lens thickness (mm)</td>
<td>Before pilocarpine 4.50 ± 0.42</td>
<td>Before pilocarpine 4.50 ± 0.46</td>
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<td></td>
<td>After pilocarpine 4.56 ± 0.43</td>
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n = 20.
rich microfibrils as well as disrupt the ultrastructure of the intact zonular bundles. Therefore, MMPs may play a role in the turnover of fibrillin microfibrils in the ocular extracellular matrix and the ciliary zonules. Latanoprost increases the activity of MMPs in the ciliary muscle, and it may do the same in the ciliary zonules, thus changing their structure and therefore their strength and elasticity. These changes could explain the decrease in ACD after treatment with latanoprost that we found in the present study.

Furthermore, collagen IV, another component of the ciliary zonules, which serves as a coating surrounding the fibrils, also is degraded by prostaglandin F$_{2\alpha}$ within the uveoscleral outflow pathway, and so this also may occur in the zonular fibers and further weaken them.

We are unaware of any other study dealing with the effects of prolonged use of a prostaglandin analogue on ACD. Only one study reported that a single application of latanoprost did not cause any significant change in the ACD 50 to 60 minutes after the dose. We believe that this is not contradictory of our results, because any biochemical changes associated with MMPs that latanoprost may cause in ocular tissue would need at least several days or weeks to appear.

The present study showed that latanoprost, a prostaglandin F$_{2\alpha}$ analogue, decreased ACD after 1 month of treatment and that the effect of pilocarpine on ACD was unchanged by latanoprost therapy, thus suggesting that their mechanisms of action differ. Pilocarpine contracts the ciliary muscles and induces the maximum possible ciliary muscle contraction. The ciliary zonules form the suspensory ligament of the lens. The zonules are anchored to the ciliary body and the lens capsule, and their main function is to mediate changes in the shape, curvature, and position of the lens. Zonular stretching induces flattening of the lens and pushes it back, and zonular relaxation enables the lens to return to its more spherical resting shape. If latanoprost-induced structural changes in the ciliary zonules weaken them more, their strength and elasticity would change as well, and this could explain our results. However, because the VA and lens thickness in our patients were unchanged despite the change in the ACD, it suggests that this change is small in terms of ocular refractive power or lens thickness.

Although the decrease in ACD induced by this drug could induce an episode of closed-angle glaucoma in susceptible individuals, the clinical evidence derived from the wide-spread use of latanoprost worldwide strongly suggests that it is a safe and effective drug for the treatment of closed-angle glaucoma.

In addition, a change in the lens position could result in an erroneous calculation of the intraocular lens (IOL) power in an eye being treated with latanoprost, when using formulas for IOL power calculation that take into account the ACD.

It is clear that more studies of the long-term effects of this drug and other prostaglandin F$_{2\alpha}$ analogues are needed, to elucidate further the effects of latanoprost on ocular structures other than the ciliary muscle and the possible clinical relevance.

References