24-Hour Control With a Latanoprost-Timolol Fixed Combination vs Timolol Alone

Anastasios G. P. Konstas, MD, PhD; Symeon Lake, MD; Athanasios I. Economou, MD; Kostantinos Kaltsos, MD; Jessica N. Jenkins, BS; William C. Stewart, MD

Objective: To evaluate 24-hour intraocular pressure (IOP) control with an evening-dosed latanoprost–timolol maleate fixed combination vs timolol alone in patients with primary open-angle glaucoma.

Methods: After a medicine-free period, qualified patients were randomized to either placebo dosed in the morning with a latanoprost-timolol fixed combination dosed in the evening or timolol alone dosed twice daily for 8 weeks. Patients were then switched to the opposite treatment for 8 weeks. At baseline and at the end of each treatment period, patients underwent IOP measurements.

Results: Both treatments reduced the IOP from untreated baseline at each time point and for the 24-hour curve (P<.001). When treatments were compared, the latanoprost-timolol fixed combination decreased the IOP more than timolol alone at each time point and for the 24-hour curve (2.9 mm Hg), and provided a lower absolute IOP at each time point (P<.001) and for the range (fluctuation) in IOP (P=.003) and for the 24-hour curve. Several adverse effects were observed more often with the latanoprost-timolol fixed combination, including ocular stinging (P=.05), conjunctival hyperemia (P=.02), and ocular itching (P=.04).

Conclusion: The evening-dosed latanoprost-timolol fixed combination may provide better IOP control than timolol alone over 24 hours and may demonstrate a narrower range of IOP fluctuation in patients with primary open-angle glaucoma.

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THE LATANOPROST–TIMOLOL maleate fixed combination (Xalacom; Pfizer, Inc, New York, NY) was commercially released in Europe in 2001. This product, and other fixed combinations, has the advantage of dosing convenience and, consequently, potentially improved compliance.

In the regulatory trials of Pfeiffer and associates¹ and Higginbotham and coworkers,² morning dosing of the fixed combination further reduced the intraocular pressure (IOP) compared with latanoprost (1.9 and 2.9 mm Hg) or timolol (1.2 and 1.0 mm Hg) dosed twice daily.

The reason for the relative lack of efficacy has not been explained. However, it may be in part because the fixed combination was instilled in the morning in both regulatory trials, whereas latanoprost alone was dosed in the evening in the study by Higginbotham et al.³ Previously, Alm and coworkers⁴ and Konstas and associates⁵,⁶ have demonstrated that nighttime dosing of latanoprost provides lower daytime pressures than morning dosing. Therefore, the study design of the regulatory trials itself may have limited the daytime efficacy and the difference from the individual components of the latanoprost-timolol fixed combination.²

Accordingly, a recent 24-hour study by Konstas and coworkers⁶ showed that the latanoprost-timolol fixed combination compared with latanoprost alone, both dosed in the evening, provided a wider margin (mean, 2.5 mm Hg) over 24 hours than the morning dosing used in the regulatory trial. However, little data still exist evaluating 24-hour pressures with the evening-dosed fixed combination compared with timolol dosed twice daily.

This trial evaluates the 24-hour efficacy and safety of the latanoprost-timolol fixed combination dosed once each evening vs timolol alone dosed twice daily in patients with primary open-angle glaucoma (POAG).

METHODS

PATIENTS

Consecutive patients were recruited for this prospective study from the Glaucoma Unit of the A University Department of Ophthalmology, AHEPA Hospital. All patients who agreed to par-
ticipate in the study and met the inclusion and exclusion criteria were enrolled. Patients included were older than 29 years; had early to moderate POAG (<12 mean deviation visual field loss attributed to glaucoma and 0.8 or better vertical cup-disc ratio); at untreated baseline, had a mean IOP at 10 AM (2 consecutive readings) higher than 23 mm Hg; had a reliable visual field (at least 2 visual fields with <30% fixation losses, false positives or negatives); had a best-corrected distance Snellen visual acuity greater than 1/10; had corneal pachymetry results within the mean±SD of 550±55 μm range; understood the study instructions and were willing to attend all follow-up appointments; were willing to comply with study medication use; and had open normal-appearing angles.

Patients excluded had risk for significant deterioration during the study; had a known history of lack of response (<10% reduction) to any topical glaucoma medication; had systemic contraindications to topical β-blockers (asthma, bradycardia, or severe congestive heart disease); had known contraindications to prostaglandins, a history of ocular herpetic disease, or cystoid macular edema; had a history of trauma, inflammation, surgery, or use of corticosteroids (within 2 months); had severe dry eyes; used contact lenses; had signs of ocular infection, except blepharitis; had a corneal abnormality that may affect IOP measurements; were unwilling to accept the risk for hypertrichosis; and were females of childbearing potential or lactating mothers.

PROCEDURES

All patients signed an informed consent agreement approved by an institutional review board before any procedures were performed. At visit 1, subjects had an ophthalmic and systemic history taken and had dilated ophthalmoscopy and automated full-threshold perimetry performed (Humphrey 24-2 test, SITA standard). At this visit, and at all other visits, the IOP was measured (2 measurements at each time point were averaged) and Snellen visual acuity testing and slitlamp biomicroscopy were performed. Qualified patients then had their glaucoma medications washed out (6 weeks for prostaglandins and 4 weeks for β-blockers) and were asked to return in 6 weeks for the baseline visit (visit 2).

At visit 2, and at all other diurnal curve visits (visits 3 and 4), patients had IOP measurements at 6 AM, 10 AM, 2 PM, 6 PM, 10 PM, and 2 AM. Patients who met the IOP inclusion requirements were randomly assigned to receive either the latanoprost-timolol fixed combination once every evening at 8PM and placebo (Tears Naturale II; Alcon Hellen, Athens, Greece) once every morning at 8:00 or timolol alone (0.5% Temserpin; MSD/Vianex, Athens) twice daily at 8 AM and 8 PM for the first 8-week treatment period.

At the end of period 1, a diurnal curve was again performed (visit 3). Patients were then switched to the second study medicine for period 2, and a diurnal curve was performed at the end of the second 8-week treatment period (visit 4). We did not include a medicine-free period between treatments to increase patient safety. In addition, we believed the 8-week treatment period was sufficient to allow for the washout of the first treatment before the efficacy measurements at the end of period 2.

The same investigators (A.G.P.K., S.L., A.I.E., and K.K.) at each site measured the IOP using the same calibrated instruments (Goldmann applanation tonometer) to perform diurnal curves of the IOP. Patients were admitted to the hospital in the morning, and measurements were recorded at 6 AM, 10 AM, 2 PM, 6 PM, 12 PM, and 2 AM. At the measurement at 12 PM, patients were awake at bed rest. The 2 AM and 6 AM IOP measurements were performed 5 minutes after wakening. Patients were encouraged to perform routine activities as much as possible within the hospital boundaries. During the study (including during examinations and IOP measurements), the investigators and staff were masked to the treatment regimen. Medicine labels were removed, and the medicines were kept in an opaque medicine vial. Patients were aware only of the colored bottle cap of the study treatment.

Patients were instructed regarding correct medication instillation and compliance. In this study, all patients were instructed to perform nasolacrimal occlusion for 1 minute after instillation of each study eyedrop. At each visit, local and systemic adverse effects that occurred during the treatment period were recorded. Adverse effects were evaluated by asking patients a general query about their state of health. Patients also were queried about their compliance to the study medicine.

STATISTICS

The primary efficacy variable was the mean level of the 24-hour pressure curve (average mean pressures measured throughout the day) between study treatments. This study had an 80% power to identify a 1.5–mm Hg difference between individual time points and between mean diurnal pressures, assuming an SD of 28.2 mm Hg between treatments.6-15 The data were evaluated by a repeated measures of analysis. The significance level was set at 5%, and a 2-way analysis was used for all tests.

The secondary efficacy variables, the level of pressure at each time point, the reduction of pressure from untreated baseline for each time point and the 24-hour pressure curve, and the maximum, minimum, and mean range of pressure (the average range of pressure over the day) between study treatments. This study had an 80% power to identify a 1.5–mm Hg difference between individual time points and between mean diurnal pressures, assuming an SD of 28.2 mm Hg between treatments.6-15 The data were evaluated by a repeated measures of analysis. The significance level was set at 5%, and a 2-way analysis was used for all tests.

RESULTS

The IOP results and reductions from baseline are shown in Table 2. The IOP results are also diagrammed in the Figure. The latanoprost-timolol fixed combination and timolol alone showed a significant IOP reduction from untreated baseline at each time point and for the 24-hour curve.

When the treatment groups were compared directly, the latanoprost-timolol fixed combination dosed in the evening demonstrated a lower absolute IOP level at each time point and for the 24-hour curve. Also, the maximum, minimum, and range of pressures were lower with the latanoprost-timolol fixed combination than with timolol alone (Table 2).

In addition, the reduction from untreated baseline was greater with the latanoprost-timolol fixed combination, compared with timolol alone, at each time point and for the 24-hour curve.

The end-of-period analyses showed the following results: at the end of period 1, the latanoprost-timolol fixed combination showed a significant IOP reduction from untreated baseline at each time point and for the 24-hour curve. The results at the end of period 1 were similar to the results at the end of period 2. The latanoprost-timolol fixed combination showed a significant IOP reduction from untreated baseline at each time point and for the 24-hour curve. The results at the end of period 1 were similar to the results at the end of period 2.

The patient characteristics are shown in Table 1. All patients had POAG and all were Greek. One patient was discontinued from the study early due to intolerance to the latanoprost-timolol fixed combination.

INTRAOCULAR PRESSURE

The IOP results and reductions from baseline are shown in Table 2 and Table 3. The IOP results are also diagrammed in the Figure. The latanoprost-timolol fixed combination and timolol alone showed a significant IOP reduction from untreated baseline at each time point and for the 24-hour curve.

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combination group had a mean±SD IOP of 16.4±2.0 mm Hg; and the timolol group, 19.2±1.4 mm Hg (n=15 for both groups). At the end of period 2, the latanoprost-timolol fixed combination group had a mean±SD IOP of 16.4±1.8 mm Hg; and the timolol group, 19.3±2.2 mm Hg (n=18 for both groups).

**ADVERSE EVENTS**

Both treatments were generally well tolerated. However, the latanoprost-timolol fixed combination demonstrated more adverse events compared with timolol alone for ocular stinging (12 vs 5; \( P = 0.05 \)), conjunctival hyperemia (7 vs 0; \( P = 0.02 \)), and ocular itching (6 vs 0; \( P = 0.04 \)). There were no other significant differences between treatment groups for any adverse event.

**COMMENT**

Previous multicenter, randomized, regulatory trials\(^1\)\(^-\)\(^2\) have demonstrated that the morning-dosed latanoprost-timolol fixed combination was more effective than either of its individual components over a 3-point diurnal curve.

Table 1. Characteristics of the 34 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.4 ± 10.8†</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
</tr>
<tr>
<td>Baseline (at 1000 h) intraocular pressure, mm Hg</td>
<td>27.3 ± 2.8†</td>
</tr>
<tr>
<td>Previous therapy</td>
<td></td>
</tr>
<tr>
<td>None (new patient)</td>
<td>12</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>5</td>
</tr>
<tr>
<td>Dorzolamide–timolol maleate fixed combination</td>
<td>4</td>
</tr>
<tr>
<td>Timolol alone</td>
<td>3</td>
</tr>
<tr>
<td>Traboprost</td>
<td>2</td>
</tr>
<tr>
<td>Timolol and latanoprost</td>
<td>2</td>
</tr>
<tr>
<td>Latanoprost-timolol fixed combination</td>
<td>1</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>1</td>
</tr>
<tr>
<td>Brimonidine and brinzolamide</td>
<td>1</td>
</tr>
<tr>
<td>Dorzolamide-timolol fixed combination</td>
<td>1</td>
</tr>
<tr>
<td>and latanoprost</td>
<td></td>
</tr>
<tr>
<td>Timolol and bimatoprost</td>
<td>1</td>
</tr>
<tr>
<td>Timolol and dorzolamide</td>
<td>1</td>
</tr>
<tr>
<td>Corneal pachymetry, µm</td>
<td>539.8 ± 24.3†</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>0.9 ± 0.2†</td>
</tr>
<tr>
<td>Mean deviation, dB</td>
<td>7.3 ± 4.5†</td>
</tr>
<tr>
<td>Cup-disc ratio</td>
<td>0.6 ± 0.09†</td>
</tr>
</tbody>
</table>

*Data are given as number of patients unless otherwise indicated.
†Data are given as mean ± SD.

Table 2. Intraocular Pressures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (N = 34)*</th>
<th>Timolol Maleate Group (N = 33)*</th>
<th>Latanoprost-Timolol Fixed Combination Group (N = 33)*</th>
<th>( P ) Value Between Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 AM</td>
<td>25.7 ± 2.7</td>
<td>20.0 ± 2.7</td>
<td>16.2 ± 2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>10 AM</td>
<td>27.2 ± 2.9</td>
<td>19.8 ± 2.8</td>
<td>16.5 ± 2.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 PM</td>
<td>25.3 ± 2.7</td>
<td>18.9 ± 2.8</td>
<td>16.4 ± 2.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 PM</td>
<td>24.8 ± 2.4</td>
<td>19.4 ± 2.0</td>
<td>16.9 ± 2.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>10 PM</td>
<td>24.9 ± 2.9</td>
<td>18.8 ± 2.7</td>
<td>16.1 ± 2.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 AM</td>
<td>23.1 ± 2.1</td>
<td>18.5 ± 1.9</td>
<td>16.2 ± 2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>24-h Curve</td>
<td>25.0 ± 2.0</td>
<td>19.3 ± 1.8</td>
<td>16.4 ± 1.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>28.1 ± 2.7</td>
<td>21.5 ± 2.3</td>
<td>18.0 ± 2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Minimum</td>
<td>22.7 ± 1.7</td>
<td>17.1 ± 1.8</td>
<td>14.8 ± 1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Range</td>
<td>5.4 ± 2.1</td>
<td>4.4 ± 1.8</td>
<td>3.2 ± 1.1</td>
<td>.003</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD intraocular pressure (measured in millimeters of mercury).
This trial evaluates the 24-hour efficacy and safety of the latanoprost-timolol fixed combination dosed once each evening vs timolol alone dosed twice daily in patients with POAG.

Compared with other adjunctive treatments, Stewart and associates noted that the latanoprost-timolol fixed combination dosed in the evening was more effective at 6 to 12 hours after dosing, and for the end of the daytime diurnal curve, than brimonidine and timolol dosed concomitantly. Furthermore, Stewart and coworkers noted that the latanoprost-based fixed combination provided equal efficacy to latanoprost and brimonidine (dosed twice daily) in a 3-point diurnal curve. Dietelhorst and associates demonstrated less efficacy by 1.1 mm Hg with once-daily morning dosing of the fixed combination vs the unfixed evening dosing of latanoprost and twice-daily timolol. In contrast, Calissendorff and coworkers found no difference in the fixed-combination pharmacokinetics vs the unfixed components.

Compared with the dorzolamide-timolol fixed combination given twice daily, Shin and associates demonstrated that the latanoprost-based fixed combination reduced the pressure by 1.0 mm Hg further over 3 diurnal time points. In contrast, Konstas and coworkers showed that the latanoprost-timolol fixed combination provided similar efficacy to the dorzolamide-timolol fixed combination over a 12-hour diurnal curve measured every 2 hours.

The present study showed that the latanoprost-timolol fixed combination and timolol alone reduced the IOP from untreated baseline at each time point and for the 24-hour pressure curve. When both treatments were compared, the latanoprost-timolol fixed combination showed significantly more reduction in IOP at each time point and for the 24-hour pressure curve. In addition, the absolute IOP at each time point and for the 24-hour pressure curve was lower with the latanoprost-timolol fixed combination compared with timolol alone.

However, this study did not include a washout period in between treatment periods. Consequently, the design of the study cannot guarantee there was no effect of the first period medicine on the second period. However, as noted in the “Results” section, “Intraocular Pressure” subsection, there did not seem to be carryover effect on the IOP being similar in both periods. In addition, the study design included an 8-week treatment, which should have allowed an adequate washout from the first treatment. Future studies might include a parallel design, which would eliminate any potential for carryover effect between treatment periods.

The extent of 24-hour reduction from untreated baseline in the present trial, for the latanoprost-timolol fixed combination (34%) and for timolol alone (23%), was consistent with past studies. However, in several regulatory trials, the extent of the pressure reduction with the latanoprost-timolol fixed combination, from timolol alone, was less than what might be anticipated with the known monotherapy efficacy of latanoprost and timolol. However, Konstas and associates noted that latanoprost alone taken at night provided a greater pressure reduction for daytime pressures. In contrast, morning-dosed latanoprost provided a greater nighttime pressure reduction. Consequently, there seems to be a peak effect with latanoprost 12 to 24 hours after dosing. This effect was also demonstrated by Konstas and coworkers for adjunctive therapy with timolol used concomitantly with latanoprost. However, to our knowledge, no trial has been performed to directly compare the 24-hour IOP efficacy of morning vs evening dosing of the latanoprost-timolol fixed combination.

Therefore, the greater 24-hour pressure reduction observed in this trial (2.9 mm Hg), compared with that observed by Pfeiffer and associates (1.9 mm Hg), with the latanoprost-timolol fixed combination vs timolol alone might be explained, at least in part, by the nighttime dosing allowing for a lower daytime pressure and a greater differential from timolol alone. However, our results, of a 2.9-mm Hg difference over a 24-hour curve (3.2 mm Hg for the average of the 3 daytime points), are similar to those of the study by Higginbotham et al., which showed a 2.9-mm Hg daytime differential between the fixed combination and timolol alone. Our findings are also consistent with those of Stewart and coworkers, who showed a further mean 3.0–mm Hg greater reduction, over a 12-hour daytime pressure curve measured every 2 hours, with the evening-dosed latanoprost-timolol fixed combination vs timolol alone.

In addition, the range of the 24-hour curve among individuals was significantly lower with the latanoprost-timolol fixed combination (3.2 mm Hg) compared with timolol alone (4.4 mm Hg). This range of 24-hour pressure for the fixed combination was less than shown in several past studies evaluating the latanoprost-timolol fixed combination (3.9–4.3 mm Hg) when morning dosing was used and is among the most narrow with medical therapy that we have observed among our past studies. The reason for the lower fluctuation of pressure with nighttime dosing may have been because, again, latanoprost instilled at night has limited the pressure increases typically observed in the daytime and helped reduce the range of IOPs.

Several historical concerns exist about using timolol at night, including a lack of an ocular hypotensive effect and an adverse influence on ocular perfusion. Brubaker and associates were unable to detect an aqueous suppressant effect from timolol during the night. Nevertheless, the present study showed a reduction of pressure at night, as shown previously by 2 of us (A.G.P.K. and W.C.S.), However, the extent of pressure reduction in the present trial at night with timolol was less than in the daytime. However, the untreated baseline pressures were also lower.

Hayreh and colleagues have suggested an adverse effect on systemic blood pressure from topical β-blockers due to reduced ocular perfusion and potentially increased ocular ischemia. Further research is needed to clarify the influence on nocturnal blood flow of timolol. Adverse events were generally few in both treatment groups. More conjunctival hyperemia was observed with the latanoprost-timolol fixed combination, as might be expected with this medication class. However, there was also more ocular stinging (35%) and itching (18%) with the latanoprost-timolol fixed combination. These adverse events have not typically been reported previously at such a high incidence.
This study suggests that the evening-dosed latanoprost-timolol fixed combination statistically decreases the IOP reduction more than timolol over 24 hours, and demonstrates a narrower range of pressure fluctuation, in patients with POAG.

This study did not directly evaluate morning vs evening dosing of the latanoprost-timolol fixed combination. Also, this study did not evaluate the long-term 24-hour efficacy or the effect of these medicines on visual variables. Such long-term studies would be important because of the goal of glaucoma therapy to preserve sight. Hopefully, continuing research will help further clarify the usefulness and efficacy of the latanoprost-timolol fixed combination.

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Correspondence: William C. Stewart, MD, Pharmaceutical Research Network, LLC, 1 Southpark Cir, Suite 110, Charleston, SC 29407 (info@prnorb.com).
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REFERENCES

5. Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.005%. Am J Ophthalmol. 1999;128:15-20.
7. Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.005%. Am J Ophthalmol. 2001;131:798-799.
14. Mundorf TK, Cate EA, Sinse CS, Otter DW, Stewart JA, Stewart WC. The safety and efficacy of switching timolol maleate 0.5% solution to timolol hemihydrate 0.5% solution given twice daily. J Ocul Pharmacol Ther. 1998;14:129-135.
15. Stewart WC, Day DG, Stewart JA, Schuur J, Latham KE. The efficacy and safety of latanoprost 0.005% once daily versus brimonidine 0.2% twice daily in open angle glaucoma or ocular hypertension. Am J Ophthalmol. 2001;131:631-635.
22. Konstas AG, Koizobolis VP, Lallos N, Christodoulakis E, Stewart JA, Stewart WC. Daytime diurnal curve comparison between the fixed combinations of latanoprost 0.005%/timolol maleate 0.5% and dorzolamide 2%/timolol maleate 0.5%. Eye. 2004;18:1264-1269.