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A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study

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• PURPOSE: To compare the intraocular pressure (IOP)-lowering effect and safety of latanoprost, bimatoprost, and travoprost in patients with open-angle glaucoma (OAG) or ocular hypertension (OH).
• DESIGN: Interventional study.
• METHODS: This 12-week, randomized, parallel-group study was conducted at 45 US sites. Previously treated patients with OAG or OH and an IOP ≥23 mm Hg in one or both eyes after washout received either latanoprost 0.005%, bimatoprost 0.03%, or travoprost 0.004% once daily in the evening. At baseline and after 6 and 12 weeks of therapy, masked evaluators measured IOP in triplicate at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM, and masked investigators graded conjunctival hyperemia before the 8:00 AM IOP measurement. The primary efficacy outcome measure was change between baseline and Week 12 in the 8:00 AM IOP (time of peak drug effect).
• RESULTS: In all, 410 of 411 randomized patients were included in intent-to-treat analyses (latanoprost, 136; bimatoprost, 136; travoprost, 138). Baseline mean 8:00 AM IOP levels were similar ($P = .772$); by week 12, reductions were observed in all 3 groups ($P < .001$ for each). Adjusted (ANCOVA) reductions in mean IOP at 8:00 AM were similar ($P = .128$) as were those at 12 noon, 4:00 PM, and 8:00 PM. Fewer latanoprost-treated patients reported ocular adverse events ($P < .001$, latanoprost vs bimatoprost), fewer reported hyperemia ($P = .001$, latanoprost vs bimatoprost), and average hyperemia scores were lower at week 12 ($P = .001$, latanoprost vs bimatoprost).
• CONCLUSIONS: Latanoprost, bimatoprost, and travoprost were comparable in their ability to reduce IOP in OAG and OH patients. Latanoprost exhibited greater ocular tolerability. (Am J Ophthalmol 2003;135: 688–703. © 2003 by Elsevier Inc. All rights reserved.)

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AMONG THE CURRENT OCULAR HYPOTENSIVE MEDICations employed in the treatment of open-angle glaucoma and ocular hypertension, prostaglandin analogues are the most potent.[1] These include the prostaglandin analogues latanoprost, bimatoprost, travoprost, and unoprostone. In the United States, latanoprost has been commercially available since 1996, with bimatoprost, travoprost, and unoprostone receiving Food and Drug Administration (FDA) approval between August 2000 and March 2001.[2] Although the precise mechanism used by these agents to lower intraocular pressure (IOP) is unclear, they are believed to act by increasing aqueous humor outflow through both the trabecular route (via Schlemm's canal and the episcleral veins) and the uveoscleral (ciliary muscle) pathway.[3–9]

Latanoprost (0.005%), bimatoprost (0.03%), and travoprost (0.004%) have been shown to be as or more effective in lowering IOP than the traditional first-line agent and standard of reference, timolol 0.5%.[10–14] Unoprostone, however, has been shown to be less effective in lowering IOP than latanoprost[15,16] and not to be more effective than timolol.[17–19] Although there is extensive documentation concerning the efficacy of the three prostaglandin analogues, especially latanoprost,[20] data determining the comparative efficacy of the three drugs in a single trial have not been reported.

The majority of the studies that compared the efficacy and safety of latanoprost and travoprost[14] or of latanoprost

differences in the IOP-lowering ability of these medications at 8 AM, the time of peak effect, and differences at other time points may have been confounded by baseline differences. The exception was a recent investigation[23] suggesting that bimatoprost may be more effective than latanoprost in reducing IOP levels. Less open to debate has been the relative frequency of several ocular adverse events, most notably ocular hyperemia, which may affect patient compliance and thus the overall effectiveness of the topical prostaglandin analogues. Compared to latanoprost, both bimatoprost and travoprost have been shown to have substantially higher rates of ocular side effects.[14,22] The present trial is the first to compare simultaneously the clinical outcomes associated with the use of latanoprost, bimatoprost, and travoprost.

METHODS

• **SETTING:** This 12-week, randomized, parallel-group, masked-evaluator study conducted at 45 sites in the United States compared the efficacy and safety of once daily administration of three commercially available prostaglandin analogues: latanoprost 0.005%, bimatoprost 0.03%, and travoprost 0.004% ophthalmic solutions. Regulatory authorities at each study site reviewed and approved the protocol in accordance with guidelines for the conduct of clinical research contained in the 1964 Declaration of Helsinki.

• **PATIENTS:** Patients were eligible for participation if they met the following inclusion criteria: age ≥ 18 years; bilateral or unilateral primary open-angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or ocular hypertension (IOP ≥ 21 mm Hg at diagnosis); current or previous (within the past 6 months) monotherapy or dual therapy with a topical ocular hypotensive agent(s); best-corrected visual acuity equal to or better than 20/200; and ability to comply with the requirements of the study protocol. All patients provided signed informed consent prior to study enrollment.

Exclusion criteria were known hypersensitivity to any component in the study medications; use of any medication known to affect IOP unless both patient and dosage were stable within the previous 3 months and no change in dosage was expected during the study; use of any investigational medications within 30 days of the screening visit; history of acute angle-closure or closed or slit open anterior chamber angle; argon laser trabeculoplasty or other ocular (globe) surgery within the previous 3 months or any previous filtering surgery (an unlasered or unfiltered eye could be enrolled as the study eye); ocular infection or inflammation within the previous 3 months; and pregnancy, lactation, or inadequate contraception.

• **TREATMENT PROTOCOL:** A screening visit examination for all patients (up to 1 month prior to the baseline visit) included a review of ocular and medical history, IOP measurement with a calibrated Goldmann applanation tonometer, Snellen visual acuity measurement, slit-lamp biomicroscopy, ophthalmoscopy, and visual field testing (automated perimetry) if not done within the past 12 months. Patients deemed eligible for the study were removed from all ocular hypotensive therapy at this time. Required washout periods prior to the baseline visit were 5 days for cholinergic agonists and carbonic anhydrase inhibitors; 2 weeks for adrenergic agonists; and 4 weeks for β-adrenergic receptor antagonists and prostaglandin analogues. For all patients previously using β-adrenergic receptor antagonists and prostaglandin analogues, IOP measurement was required as a safety check after 2 weeks of washout; observed IOP levels considered potentially hazardous resulted in patients being excluded from the study.

Study visits occurred at baseline and after 2, 6, and 12 weeks of therapy. At the baseline visit, which followed the washout period, masked evaluators performed three IOP measurements in each eye, alternating between eyes, and starting with the right eye at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM. The mean of these IOP measurements at each time point was used in statistical analyses. Either one or both eyes of a patient could be enrolled as study eyes. An eye was eligible if the mean IOP was ≥23 mm Hg at the 8:00 AM baseline measurement. For patients having both eyes enrolled, the mean of the IOP readings in both eyes was used as the patient's IOP in the analyses. In patients with bilateral disease with only one eye that met all eligibility criteria (study eye), the other eye also could be treated with study drug provided that no exclusion criteria existed for that eye. If both eyes met all eligibility criteria, both were enrolled as study eyes.

Study medications were packaged in commercially available labeled containers manufactured by Pharmacia Corporation (latanoprost), Allergan (bimatoprost), and Alcon Laboratories (travoprost). To preserve masking, each container was overpackaged in an opaque black vial and then sealed in a patient kit with tamper-evident strips; the name of the drug was not included on kit labels. A designated, unmasked coordinator (who did not perform any study evaluations or assessments) at each study center received randomization codes and prepackaged clinical supplies from Pharmacia Clinical Supply Logistics (Kalamazoo, Michigan, USA), and dispensed the medication kits. The coordinator was responsible for storing each medication kit according to its respective product package insert.

Following the 8:00 PM baseline measurement, eligible patients were randomly assigned within each study center to one of three treatment groups in a 1:1:1 ratio: latanoprost 0.005%, bimatoprost 0.03%, or travoprost 0.004%. One patient medication kit was dispensed to each eligible patient at the baseline visit and another at the week 6

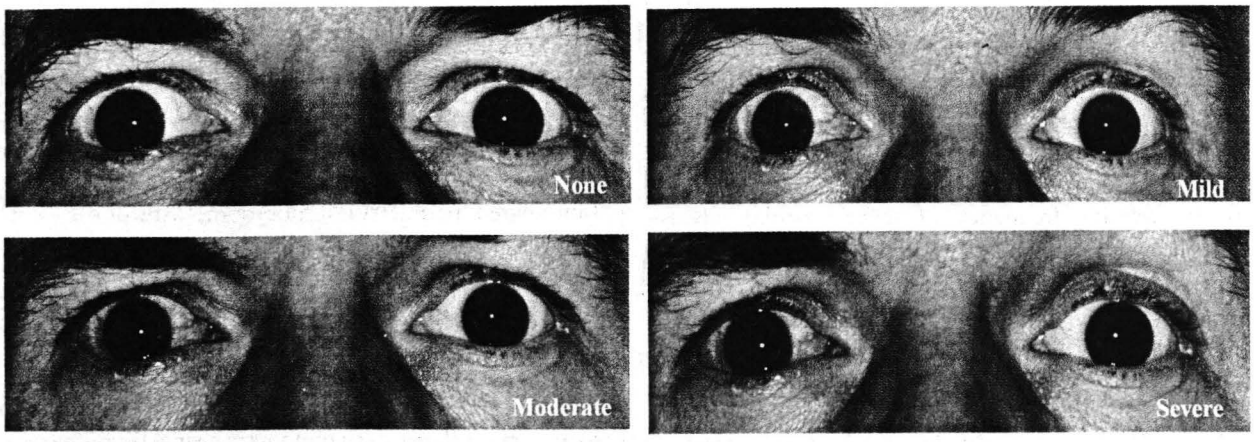

FIGURE 1. Standard photographs used to assess grades of conjunctival hyperemia.

visit; patients were instructed to return all study medications at week 12 or at the final visit for those discontinuing the study early. Patients were reminded to change study medication bottles every 4 weeks. Each medication was to be instilled daily at 8:00 PM, and no other IOP-reducing therapy was permitted. Instillation of study medication began on the evening of the baseline visit. Physician investigators (hereafter called investigators) and evaluators remained masked to treatment throughout the study; patients were the only ones aware of their treatment assignments and were cautioned not to reveal the treatment assignment to masked study-site personnel. At weeks 2, 6, and 12, investigators noted on the case report form whether or not masking had been maintained. The statistician also was masked until the database was closed.

Intraocular pressure was measured at any time during the day at week 2 and at 8:00 AM, 12 noon, 4:00 PM, and 8:00 PM at weeks 6 and 12 (or at time of earlier discontinuation). As at baseline, masked evaluators performed three IOP measurements in each eye, alternating between eyes, and starting with the right eye at each specified time point. At weeks 6 and 12, patients were questioned to ensure that the last eyedrop was administered the evening before the visit. The mean of the three IOP measures for each eye at each time point was used in statistical analyses.

At baseline and weeks 6 and 12, an investigator masked to treatment completed a conjunctival hyperemia grading scale before the 8:00 AM IOP measurement; at week 2, grading was performed prior to tonometry. The presence and severity of hyperemia were assessed by the method used in several phase 3 registration trials.[10–12] Each eye was compared with standard photographs showing conjunctival hyperemia of grades 0, 1, 2, and 3 (none, mild, moderate, and severe, respectively) (Figure 1); the scale included values of 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0. In addition, at every visit, the same investigator asked patients whether they or anyone else had noticed any redness in his or her eye(s) since the last visit and, if so, to what symptom was graded with the following responses: not at all, a small amount, a moderate amount, or a great amount. Investigators recorded patients' responses.

Throughout the study, any undesired medical occurrence regardless of relationship to treatment was considered an adverse event and was monitored. Defined criteria were used to grade the intensity of each adverse event and to classify the event as serious or nonserious. Any adverse event considered serious, related to study medication and persistent, or any ocular adverse event present at the end of study treatment (week 12) resulted in patients being followed up for 2 weeks after the final visit. Follow-up of serious adverse events considered to be related to a study medication continued until events were resolved or deemed chronic or stable.

• MAIN OUTCOME MEASURES AND ANALYSES: The Fisher least significant difference procedure was used to compare treatment groups.[24] Continuous variables were tested for treatment group differences using one-way analysis of variance (ANOVA) with treatment (latanoprost, bimatoprost, or travoprost) as the independent variable. If the overall treatment effect was not significant ($P > .05$), it was concluded that no difference existed between treatment means. If the overall treatment effect was significant ($P \leq .05$), pairwise comparisons of treatment means were performed using t tests, with the significance of each set at the .05 level.

The primary efficacy outcome, mean change between baseline and week 12 in IOP measurements obtained at 8:00 AM (time of peak drug effect), was analyzed using the above procedure, but with the analysis of covariance model (ANCOVA), with baseline IOP as the covariate and treatment and center as factors. If the overall treatment effect was significant, pairwise comparisons of treatment means were performed using contrasts. The 95% confidence interval (CI) of the difference in the mean change was calculated based on the ANCOVA model. This

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