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ORIGINAL RESEARCH

Ocular surface disease in patients with glaucoma or ocular hypertension treated with either BAK-preserved latanoprost or BAK-free travoprost

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Purpose: The preservative benzalkonium chloride (BAK) may adversely affect ocular surface health. This study evaluated symptoms of ocular surface disease (OSD) in patients previously treated with a BAK-preserved therapy to lower their intraocular pressure, who either continued that therapy or switched to a BAK-free therapy.

Methods: Eligible adult patients with ocular hypertension or open-angle glaucoma that had been controlled with BAK-preserved latanoprost 0.005% monotherapy (Xalatan®) for at least one month and had a score of ≥ 13 (0 = none, 100 = most severe) on the Ocular Surface Disease Index (OSDI) questionnaire were entered into this prospective, double-masked, randomized, active-controlled, multicenter trial. By random assignment, patients either continued with BAK-preserved latanoprost 0.005% or transitioned to BAK-free travoprost 0.004% (Travatan Z® ophthalmic solution). OSDI scores were assessed again after six and 12 weeks.

Results: For the 678 evaluable patients, mean change in OSDI score from baseline to week 12 favored the travoprost 0.004% BAK-free group, but was not statistically different between groups ($P = 0.10$). When patients with mild OSD at baseline were assessed after 12 weeks, the mean OSDI score was significantly lower ($P = 0.04$) in the BAK-free travoprost 0.004% group (score = 11.6 ± 10.8 units) than in the BAK-preserved latanoprost 0.005% group (score = 14.4 ± 11.9 units), and a significantly larger percentage ($P < 0.01$) improved to normal OSDI scores in the BAK-free travoprost 0.004% group (62.9% of group) than in the BAK-preserved latanoprost 0.005% group (47.0% of group). Patients pretreated with BAK-preserved latanoprost 0.005% for >24 months were significantly more likely ($P = 0.03$) to improve to a normal OSDI score after 12 weeks if they were switched to BAK-free travoprost 0.004% (47.9% of group) than if they remained on BAK-preserved latanoprost 0.005% (33.9% of group).

Conclusions: Switching from BAK-preserved latanoprost 0.005% to BAK-free travoprost 0.004% yielded significant improvements in symptoms of OSD in patients with glaucoma or ocular hypertension.

Keywords: ocular surface, glaucoma, benzalkonium chloride, prostaglandin analog, preservative

Introduction

Most of the currently available topical treatments for elevated intraocular pressure (IOP), including latanoprost 0.005%, are preserved with benzalkonium chloride (BAK).[1] Chronic exposure to BAK-preserved IOP-lowering medications has been associated with increased frequency of patient-reported symptoms of ocular discomfort, including burning, stinging, foreign body sensation, and dry eye sensation.[2] In vitro, BAK-preserved latanoprost 0.005% and BAK-preserved travoprost 0.004% are both toxic to ocular cells, whereas BAK-free travoprost 0.004% is not.[3]

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In animal models, BAK-free travoprost 0.004% did not affect goblet cell numbers[4] or corneal epithelial cells,[5,6] whereas BAK-preserved latanoprost 0.005% was shown to cause losses of goblet cells[4] as well as pathologic changes in the corneal epithelium.[5,6] In humans, chronic exposure to BAK-preserved topical IOP-lowering medications was associated with signs of adverse effects on the ocular surface, including instability of the tear film,[7–9] reduced density of superficial epithelial cells,[7] disruption of corneal epithelial barrier function,[8] and conjunctival inflammation.[9] Adverse reactions induced by BAK-preserved medications may be reversible in glaucoma patients who are switched to BAK-free medications.[2] For these reasons, many researchers and clinicians have recommended BAK-free IOP-lowering medications.[1–9]

BAK-induced changes may manifest as symptomatic ocular surface disease (OSD) in medically treated glaucoma patients.[10,11] OSD is an umbrella term that includes dry eye, lid disease, conjunctivitis, and keratitis.[12] Although OSD is seen in approximately 15% of the general elderly population,[13] it has been reported to occur in 48% to 59% of patients with medically treated glaucoma.[10,11] A higher incidence[10] and severity[11] of OSD has been reported in patients who received multiple BAK-preserved treatments concomitantly than in patients who were treated with only one BAK-preserved treatment. Antihypertensive medications with alternative preservative systems (other than BAK) could help to maintain the long-term ocular surface health of patients with glaucoma, and could avoid inducing or aggravating OSD.

In a previous large multicenter clinical trial of patients with glaucoma who had been previously treated with either latanoprost 0.005% or bimatoprost 0.03%, and who needed alternative therapy due to tolerability issues, a switch to BAK-free travoprost 0.004% resulted in improvement in OSD symptoms that were both clinically and statistically significant, and maintained equal or better control of IOP.[14] However, that study was not conducted in a parallel, randomized, masked fashion. The objective of this current multicenter, double-masked, randomized, controlled study was to quantify changes in symptoms of OSD after randomizing patients with open-angle glaucoma or ocular hypertension who were previously treated with latanoprost 0.005% preserved by 0.02% BAK (Xalatan® ophthalmic solution; Pfizer Inc., NY) either to remain on BAK-preserved latanoprost 0.005% or to change to BAK-free travoprost 0.004% (Travatan Z® ophthalmic solution; Alcon Laboratories, Inc., Fort Worth, TX).

Methods

This was a prospective, double-masked, randomized, active-controlled clinical trial, conducted at 66 clinics in the US. The protocol was approved by the appropriate review boards at all participating institutions, and the trial was conducted in accordance with the tenets of the Declaration of Helsinki. All participating patients signed a written informed consent form.

General entry criteria

Eligible patients were at least 18 years of age, had ocular hypertension or primary open-angle glaucoma (with or without pigment dispersion or a pseudoexfoliation component), and had IOP that was adequately controlled on latanoprost 0.005% monotherapy for at least one month prior to enrollment. Adequate IOP control was determined for each patient by the enrolling investigator, and was defined as being both stable and safe for that patient. General ocular health exclusion criteria included the following: corneal abnormalities that could prevent accurate applanation tonometry; any intraocular surgery or ocular trauma within the previous six months; any ocular laser surgery within the previous three months; progressive retinal or optic nerve disease; severe central visual field loss; or visual acuity worse than 0.6 logMAR in either eye. Patients were also excluded if they had used any ocular medications (other than latanoprost 0.005% or artificial tears) within seven days of the screening visit, or if they had taken any systemic medication for less than 30 days of stable dosing before the screening visit. Women of childbearing potential were allowed to participate in the trial only if they were not breastfeeding, were not pregnant or planning to become pregnant, and were using adequate birth control during the study. All patients were required to be willing and able to abstain from the use of any other topical ophthalmic eye drops, other than assigned study medication, for the duration of the study.

Ocular surface entry criteria

Exclusion criteria related to ocular surface health were as follows: OSD that had previously been treated with punctal plugs, punctal cautery, topical cyclosporine A, or topical corticosteroids; suspected or diagnosed Sjögren's syndrome; prior corneal surgery (including keratorefractive surgery) within the previous one year; presence or history of clinically significant blepharitis within the previous two years; any history of other ocular inflammatory disease (eg, rosacea that affected the ocular adnexa or herpes

simplex virus keratitis); seasonal ocular allergies expected within the study period; and any contact lens wear or corticosteroid use within the 30 days before the screening visit.

All potential patients were screened using the Ocular Surface Disease Index (OSDI) questionnaire. The OSDI is a validated, self-administered instrument for assessing the presence and severity of OSD symptoms.[15] The OSDI questionnaire includes 12 questions about the respondent's past-week experience with ocular symptoms, vision-related functioning, and environmental triggers.[15,16] Questions assessed whether respondents had eyes that felt gritty, painful, sore, or sensitive to light; whether they had blurred or poor vision; whether they experienced limitations with reading, driving at night, watching television, or working with a computer or bank machine; and whether their eyes felt uncomfortable in windy conditions, in areas with low humidity, or in air-conditioned places.[16] Response options for each question were "all of the time" (score = 4), "most of the time" (score = 3), "half of the time" (score = 2), "some of the time" (score = 1), and "none of the time" (score = 0).[15] Questions about vision-related functioning or environmental triggers could also be answered with "not applicable", in which case that question was not factored into the final score calculation. The total OSDI score was calculated for each patient using the methods described by the OSDI originators,[15] as follows:

$$\text{OSDI score} = \frac{(\text{sum of scores for all questions answered}) \times 25}{\text{Total number of questions answered}}$$

The final total OSDI score could range from 0 to 100, with the OSDI scores classified as ≤12 = normal, 13–22 = mild OSD, 23–32 = moderate OSD, and ≥33 = severe OSD.[17] To be eligible for inclusion in the study, patients were required to have an OSDI score of 13 or higher.

All potential patients were screened with corneal fluorescein staining. Corneal fluorescein staining was conducted according to each investigator's standard procedure, using their standard staining agent. Each cornea was scored on the following scale, which was designed to assess staining over the entire corneal surface with no specification of corneal regions: 0 = absent (no staining), 1 = mild (a few punctate regions of staining, but less than 10% coverage of the corneal surface), 2 = moderate (10%–50% coverage of the corneal surface), or 3 = severe (more than 50% coverage of the corneal surface). To be eligible for the study, patients were required to have a corneal fluorescein staining score of 1 or higher.

Enrollment and masked randomization

Patients who met all entry criteria and who reported using latanoprost 0.005% on the evening prior to the screening/enrollment visit were invited to participate. At the enrollment visit, the informed consent form was signed, comprehensive medical and ophthalmic histories were obtained, the OSDI questionnaire was completed, and an ocular examination was performed (including visual acuity determination, slit-lamp inspection of the anterior segment, corneal fluorescein staining, Goldmann tonometry, and dilated fundus examination). Women of childbearing potential provided urine samples for pregnancy tests.

The targeted enrollment was approximately 700 patients (350 per group) in order to obtain approximately 650 evaluable patients (325 per group). Power calculations (using a two-sample *t*-test with two-sided alpha = 0.05) indicated that, with 325 patients per treatment group, the study would have at least 90% power to detect a difference between treatment groups that was >5 units on the OSDI questionnaire, assuming a common standard deviation of 19 units in the mean change from baseline OSDI score.

At the completion of the first visit, enrolled patients were randomized to an intervention whereby they either continued on therapy with BAK-preserved latanoprost 0.005% or were transitioned to therapy with BAK-free travoprost 0.004% ophthalmic solution. BAK-preserved latanoprost 0.005% was the commercially available Xalatan® ophthalmic solution, which is preserved using 0.02% BAK. BAK-free travoprost 0.004% was the commercially available Travatan Z® ophthalmic solution containing the proprietary sofZia® preservative, which is an ionic buffer system containing borate, propylene glycol, sorbitol, and zinc chloride.

If both eyes met all of the eligibility criteria, both eyes were treated with the same test medication; otherwise, only the eligible eye was treated. At the study site, the enrolling clinician assigned a number to the patient, and then called an interactive voice response system that was hosted by the study sponsor in order to receive a kit number. These kit numbers had been randomized by the study sponsor using statistical software (SAS Institute, Cary, NC). The patient received the assigned kit of study medication. Within the kits, all medications (whether BAK-preserved latanoprost 0.005% or BAK-free travoprost 0.004%) were packaged in identical oval 4 mL polypropylene dropper bottles. Each patient received two bottles of the assigned study medication and was instructed to instill one drop of study medication in the study eye(s) once daily in the evening. In case of a medical emergency that required information about the study

medication, the investigator or a designee could request unmasking of the test medication by calling the interactive voice response system.

Efficacy and safety assessments

Patients returned six weeks (42 ± 7 days) after enrollment for the second study visit, and 12 weeks (90 ± 7 days) after enrollment for the third study visit. Both of these visits were scheduled at approximately the same time of day as the entry visit for each patient. At both follow-up visits, an interval medical history was obtained and any adverse events were assessed, the OSDI questionnaire was completed, and an ocular examination was conducted, consisting of visual acuity, slit-lamp anterior segment inspection, corneal fluorescein staining, and Goldmann tonometry. At the 12-week visit, a dilated fundus examination was conducted, and women of childbearing potential provided urine samples for pregnancy tests.

The primary efficacy variable was the mean change in OSDI scores between the entry visit and the 12-week follow-up visit. A secondary efficacy variable was the percentage of patients with a corneal fluorescein staining score of 0. Exploratory efficacy variables that were assessed at the 12-week follow-up visit were the proportion of patients who had a normal OSDI score (≤12 units), percentage of patients with a ≥10-point improvement from baseline OSDI score, OSDI outcomes stratified by duration of pretreatment with BAK-preserved latanoprost 0.005% before entering the study, and OSDI outcomes stratified by severity of baseline OSDI (mild, moderate, or severe). Safety variable assessments included best-corrected visual acuity, slit lamp evaluations, IOP, dilated fundus examinations, and adverse events.

Table 1 Baseline values and demographics for the intent-to-treat population

	Travoprost 0.004% BAK-free, n = 343	BAK-preserved latanopros 0.005%, n = 335	Overall population n = 678
Age, n (%)			
18–64 years	131 (38.2%)	114 (34.0%)	245 (36.1%)
≥65 years	212 (61.8%)	221 (66.0%)	433 (63.9%)
Gender, n (%)			
Male	132 (38.5%)	105 (31.3%)	237 (35.0%)
Female	211 (61.5%)	230 (68.5%)	441 (65.0%)
OSDI category, n (%)			
Normal*	2 (0.6%)	2 (0.6%)	4 (0.6%)
Mild	141 (41.1%)	136 (40.6%)	277 (40.9%)
Moderate	91 (26.5%)	85 (25.4%)	176 (26.0%)
Severe	109 (31.8%)	112 (33.4%)	221 (32.6%)
Duration of BAK-preserved latanoprost pretreatment, n (%)			
Total with data available†	311 (90.7%)	300 (89.6%)	611 (90.1%)
Without data available	32 (9.3%)	35 (10.4%)	67 (9.9%)
1–6 months	109 (31.8%)	100 (29.9%)	209 (30.8%)
6–24 months	78 (22.7%)	87 (26.0%)	165 (24.3%)
>24 months	124 (36.2%)	113 (33.7%)	237 (35.0%)

Notes: *These patients were enrolled due to an error in calculating the baseline OSDI score; †Of those patients who could recall their start date with BAK-preserved latanoprost 0.005%.

Abbreviations: OSDI, Ocular Surface Disease Index; BAK, benzalkonium chloride.

Statistical analysis

Continuous variables were assessed using a two-sample *t*-test with two-sided $\alpha = 0.05$, and categoric variables were assessed by Chi-square test with $\alpha = 0.05$. The null hypothesis stated that no relationship existed between BAK-preserved treatment and change in OSDI score. The alternative hypotheses stated that BAK-preserved latanoprost 0.005% had an adverse impact on OSD, which might accrue over a longer duration of BAK-preserved latanoprost 0.005% treatment, but might be reversible to some degree by transition to BAK-free travoprost 0.004%, especially in patients with mild OSDI. Unless otherwise specified, outcome values are presented as mean ± standard deviation in text, and as mean ± standard error in figures.

Results

Baseline clinical and demographic data

A total of 724 patients were enrolled, 678 of whom were evaluable for the intent-to-treat (ITT) analysis. Four of the ITT patients had normal OSDI scores at baseline, which was an exclusion criterion, but they received study medication and thus were evaluated with the rest of the population. As shown in Table 1, the two treatment groups were statistically similar (all $P > 0.05$) in the baseline parameters of gender, age, OSDI category, and duration of exposure to BAK-preserved latanoprost 0.005% before entry into the study. The first visit of the first patient was in July 2008, and the final analysis date was in June 2009. Participant flow through the study is shown in Figure 1.

Mean change in OSDI scores

For the patients who had mild OSD at baseline, the mean OSDI score at the 12-week time point was significantly lower ($P = 0.04$) in patients randomized to BAK-free travoprost 0.004% (11.6 ± 10.8 units) than in patients who continued on BAK-preserved latanoprost 0.005% (14.4 ± 11.9 units), as shown in Figure 2. For the overall cohort of patients with all baseline OSDI scores, mean OSDI scores at the 12-week

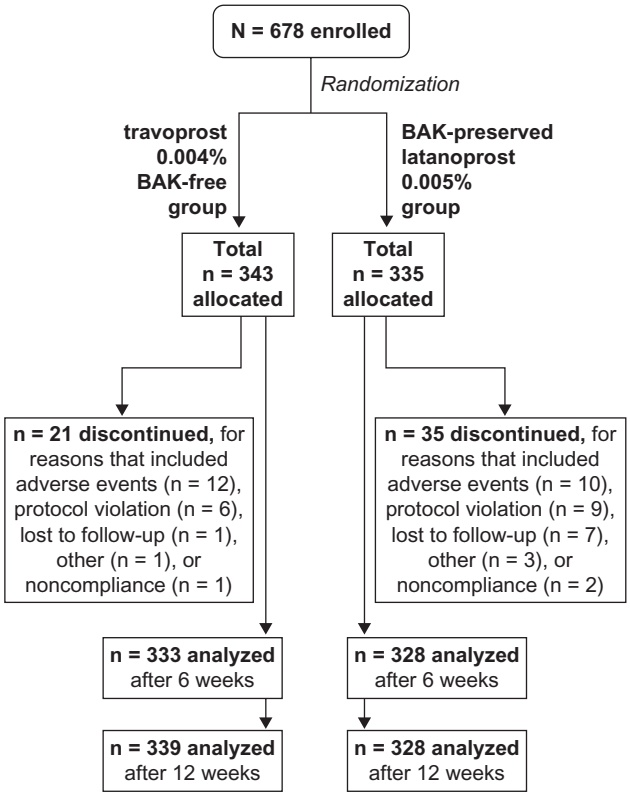

Figure 1 Participant flow through the study. When possible, patients who discontinued treatment were analyzed before exiting the study, so discontinuation and analysis numbers are not mutually exclusive.
Abbreviation: BAK, benzalkonium chloride.

time point were not statistically different between the groups, ie, 18.4 ± 16.0 for 339 patients in the BAK-free travoprost 0.004% group, and 19.4 ± 15.3 for 328 patients in the BAK-preserved latanoprost 0.005% group.

When normalized to baseline values, the mean change in OSDI score from the entry visit to the 12-week follow-up visit was not significantly larger ($P = 0.10$) for the patients with mild OSD at baseline who were randomized to BAK-free travoprost 0.004% (–5.0 ± 10.8 units, n = 140) than for patients with mild OSD at baseline who continued on BAK-preserved latanoprost 0.005% (–2.7 ± 12.1 units, n = 132), as shown in Figure 3. The mean change from baseline mild OSDI score to score at week 12 was statistically different, from zero change in both treatment groups ($P = 0.01$ in the BAK-preserved latanoprost 0.005% group and $P < 0.0001$ in the BAK-free travoprost 0.004% group). Mean change from baseline OSDI scores in the "baseline–moderate" and "baseline–severe" groups were not statistically different between the treatment groups. For the overall cohort of patients with all baseline OSDI scores, mean changes in OSDI scores at the 12-week time point were not statistically different between groups (–11.3 ± 17.2 for the 339 patients in the BAK-free travoprost

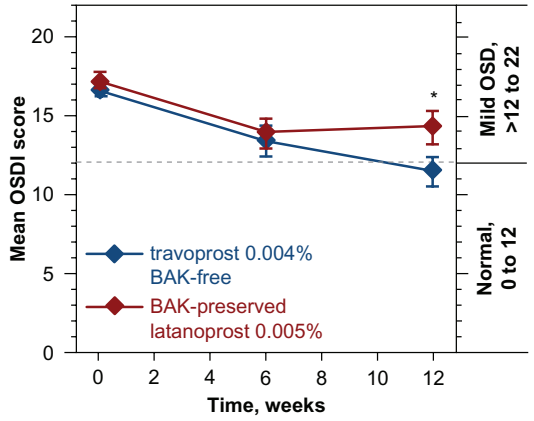

Figure 2 Mean scores on the OSDI questionnaire for the patients who had mild OSD at baseline. Error bars represent standard error of the mean. *$P < 0.05$. In the BAK-free travoprost group, patient numbers were 141 at baseline, 135 at week 6, and 140 at week 12. In the BAK-preserved latanoprost group, patient numbers were 136 at baseline, 134 at week 6, and 132 at week 12.
Abbreviations: BAK, benzalkonium chloride: OSDI, Ocular Surface Disease Index; OSD, ocular surface disease.

0.004% group and –11.4 ± 17.4 for the 328 patients in the BAK-preserved latanoprost 0.005% group).

Patients improving to normal OSDI scores

The percentage of patients who had mild OSDI scores at baseline and who improved to normal OSDI scores after 12 weeks was significantly larger ($P < 0.01$) in the BAK-free travoprost

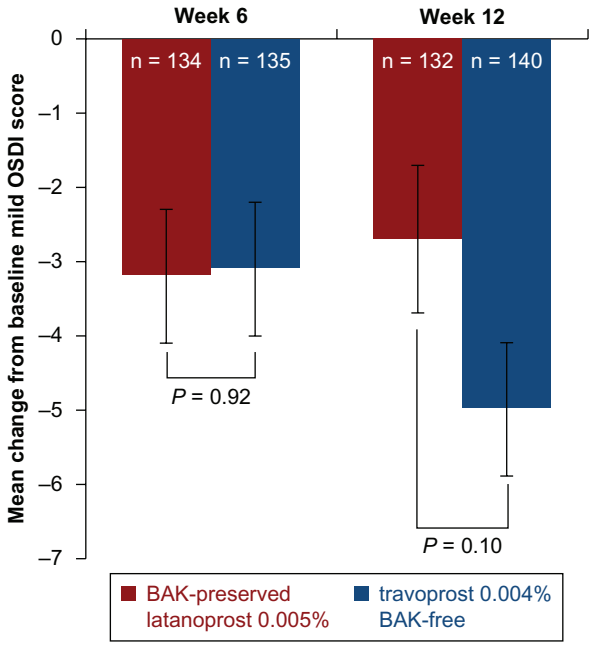

Figure 3 Mean change from baseline scores on the OSDI questionnaire for the patients who had mild ocular surface disease at baseline. Error bars represent standard error of the mean.
Abbreviations: BAK, benzalkonium chloride; OSDI, Ocular Surface Disease Index.

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