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Ocular Surface Tolerability of Prostaglandin Analogs in Patients with Glaucoma or Ocular Hypertension

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Abstract

Purpose: To compare the ocular surface tolerability of latanoprost 0.005% preserved with 0.02% benzalkonium chloride (BAK), bimatoprost 0.03% preserved with 0.005% BAK, and travoprost 0.004% preserved with the proprietary preservative system sofZia in patients previously treated with latanoprost.
Methods: This randomized, multicenter, investigator-masked, parallel-group study enrolled patients with open-angle glaucoma or ocular hypertension who had been on latanoprost monotherapy for at least 4 weeks. At baseline, patients were randomized to receive once-daily bimatoprost ($n = 35$), latanoprost ($n = 38$), or travoprost ($n = 33$) monotherapy for 3 months. Follow-up visits were at week 1, month 1, and month 3. The primary outcome measure was physician-graded conjunctival hyperemia at month 3. Secondary outcome measures included corneal staining with fluorescein and tear breakup time (TBUT).
Results: There were no significant differences among the treatment groups in conjunctival hyperemia scores, corneal staining, or TBUT at the latanoprost-treated baseline or at any follow-up visit. Baseline mean (standard error of the mean) values were as follows—conjunctival hyperemia: bimatoprost 0.74 (0.10), latanoprost 0.74 (0.11), travoprost 0.86 (0.12), $P = 0.692$; corneal staining: bimatoprost 0.59 (0.12), latanoprost 0.70 (0.13), travoprost 0.48 (0.11), $P = 0.423$; TBUT (in seconds): bimatoprost 9.1 (1.0), latanoprost 8.6 (0.8), travoprost 7.9 (0.8), $P = 0.578$. Month 3 values were as follows—conjunctival hyperemia: bimatoprost 0.80 (0.12), latanoprost 0.74 (0.10), travoprost 0.98 (0.13), $P = 0.340$; corneal staining: bimatoprost 0.71 (0.78), latanoprost 0.47 (0.64), travoprost 0.36 (0.62), $P = 0.110$; TBUT (in seconds): bimatoprost 9.7 (5.3), latanoprost 9.2 (5.3), travoprost 9.7 (6.3), $P = 0.909$.
Conclusions: There were no significant differences among bimatoprost (preserved with 0.005% BAK), latanoprost (preserved with 0.02% BAK), and travoprost (preserved with sofZia) in objective clinical measures of ocular tolerability, including physician-graded hyperemia, corneal staining, and TBUT after 3 months of treatment. Longer-term studies are needed to further evaluate the ocular surface tolerability of these prostaglandin analogs.

Introduction

The prostaglandin analogs (PGAs) latanoprost, bimatoprost, and travoprost are commonly used as first-line therapy for lowering intraocular pressure (IOP) in glaucoma and ocular hypertension (OHT). In addition to effectively lowering IOP, these medications have a favorable safety and tolerability profile and are conveniently dosed once daily.[1] The most common side effect of topical PGAs is conjunctival hyperemia, which is noninflammatory, typically transient, and not associated with sequelae.[2–4]

Each of the PGAs is administered from a multidose bottle that contains a preservative to ensure sterility, but the type of preservative and its concentration differ among the PGAs. Latanoprost 0.005% (Xalatan; Pfizer Inc., New York, NY) and bimatoprost 0.03% (Lumigan; Allergan, Inc., Irvine, CA) are each preserved with benzalkonium chloride (BAK) at concentrations of 0.02% and 0.005%, respectively, while travoprost 0.004%, which was introduced in a formulation (Travatan) preserved with 0.015% BAK, is now available in a formulation (Travatan Z) preserved with the proprietary preservative system sofZia (Alcon Laboratories, Inc., Fort Worth, TX).

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BAK remains the most commonly used preservative in ophthalmic medications because of its broad-spectrum bactericidal and bacteriostatic activity, compatibility with other formulation components, and activity at physiological pH.[5–7] While corneal toxicity secondary to BAK has been demonstrated in prior studies *in vitro*[8,9] as well as in some rabbit models,[7,10–14] these studies may not accurately replicate the ocular surface conditions in patients undergoing standard treatment. In rabbits, BAK is absorbed into the conjunctiva where it may remain for 14 days,[15] yet there is no evidence for accumulation of BAK in human conjunctiva. Although some rabbit models have used once-daily dosing to mimic the clinical dosing regimen,[13,14] the models do not necessarily account for differences in blink rate and ocular surface clearance of topical preservatives in human eyes. Similar deleterious surface effects have not been seen in dogs,[16] and further study is needed to determine the effects of preservatives in ophthalmic solutions in human eyes.[14]

The aim of this study was to compare the ocular surface tolerability of latanoprost 0.005% preserved with 0.02% BAK, bimatoprost 0.03% preserved with 0.005% BAK, and travoprost 0.004% preserved with sofZia in patients with glaucoma or OHT.

Methods

This was a randomized, 3-month, investigator-masked, parallel-group comparison study carried out at 9 sites. The study was approved by an institutional review board at each site and adhered to Health Insurance Portability and Accountability Act regulations and Good Clinical Practice guidelines as outlined in the Declaration of Helsinki. All patients provided written informed consent. The study was registered with the identifier NCT00539526 at www.clinicaltrials.gov.

Patients at least 18 years old with a diagnosis of open-angle glaucoma or OHT who had been on bilateral latanoprost monotherapy for at least 4 weeks were eligible for the study. Patients on latanoprost and 1 adjunctive medication at screening were also eligible, but were required to undergo a 4-week washout of the adjunctive medication before the baseline visit. Primary exclusion criteria included uncontrolled systemic disease, use of bimatoprost or travoprost within the previous 6 months, required use of ocular medications other than the study medications during the study (intermittent use of BAK-free artificial tears was permitted), corneal scarring, history of refractive surgery, use of contact lenses, and punctal plug use. With the intention that the study population reflect glaucoma and OHT patients typically seen in clinical practice, there was no selection for patients with dry eye disease, but patients with dry eye were not excluded from the study.

At the baseline visit, patients were randomized in a 1:1:1 ratio to monotherapy with bimatoprost 0.03% (Lumigan; Allergan, Inc.), latanoprost 0.005% (Xalatan; Pfizer Inc.), or travoprost 0.004% with sofZia (Travatan Z; Alcon Laboratories, Inc.) for 3 months. To maintain efficacy and achieve investigator masking, patients were provided with identically appearing sealed cartons, labeled with the patient randomization number, which contained marketed bottles of the study medications, and patients were instructed not to disclose their study medication to the investigator or office medication in each eye once daily in the evening between 7 and 9 PM.

The study protocol called for visits at baseline, week 1, month 1, and month 3 between 11 AM and 1 PM. The primary outcome measure was conjunctival hyperemia at month 3. Hyperemia was evaluated by gross visual inspection and graded by the investigator by comparison with color photographic standards on the Allergan bulbar hyperemia grading guide using a scale of 0 = none (normal), 0.5 = trace (trace flush, reddish pink), 1 = mild (mild flush, reddish color), 2 = moderate (bright red color), and 3 = severe (deep, bright diffuse redness). Secondary outcome measures included corneal staining with fluorescein, tear breakup time (TBUT), and IOP. Corneal staining of superficial punctate keratopathy was graded on a scale of 0 = none (no findings), 0.5 = trace (1–5 puncta), 1 = mild (6–20 puncta), 2 = moderate (>20 puncta), and 3 = severe (too many puncta to count) at each visit. TBUT (in seconds) and IOP (2 consecutive measurements for each eye) were measured at each visit. IOP was measured to ensure patient safety and was collected at only a single timepoint at each visit.

The analyses of outcomes were based on observed values in the per-protocol (PP) patient population of all patients with no major protocol violations. Among-group differences in outcome measures were analyzed using analysis of variance. Average values from both eyes were used in each analysis. Categorical variables were analyzed using the chi-square test or the Fisher exact test. All statistical tests were 2-tailed with the alpha level for statistical significance set at 0.05.

Results

The study enrolled 106 patients who were on topical latanoprost monotherapy for at least 4 weeks at the baseline visit. There were no significant differences among the treatment groups in age, sex, race, iris color, or ocular diagnosis at baseline (Table 1). Most of the patients were women (58%), Caucasian (60%), and found to have open-angle glaucoma (86%). There was also no significant difference among treatment groups in patient history of exposure to topical IOP-lowering medications. Most of the patients had been on IOP-lowering medication for at least 1 year before the baseline visit (Table 1).

After randomization to bimatoprost, latanoprost, or travoprost monotherapy, 99 patients (93.4%) completed the 3-month study without any significant protocol violations and were included in the PP patient population used for analyses. Seven patients (3 in the bimatoprost group, 2 in the latanoprost group, and 2 in the travoprost group) discontinued from the study. Reasons for patient discontinuations were adverse events (swollen eyelids, $n = 1$ and headache, $n = 1$) and personal reasons ($n = 1$) in the bimatoprost group, adverse events (red/dry/gritty eyes, $n = 1$) and loss to follow-up ($n = 1$) in the latanoprost group, and adverse events (redness, $n = 1$) and missed visits ($n = 1$) in the travoprost group.

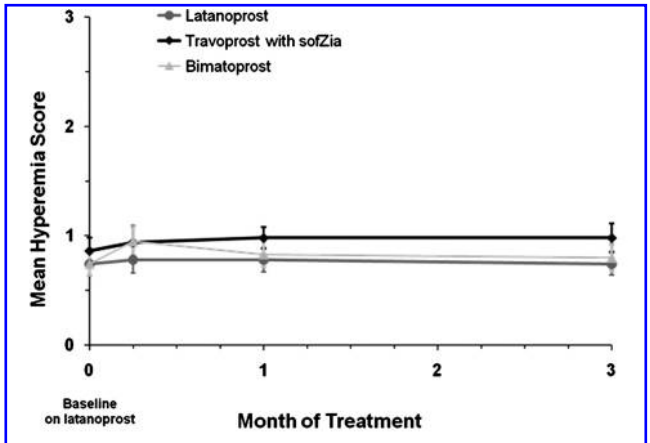
The investigators graded conjunctival hyperemia, corneal staining with fluorescein, and TBUT at each study visit. At latanoprost-treated baseline, the mean [standard error of the mean (SEM)] conjunctival hyperemia score was 0.74 (0.10) in the bimatoprost group, 0.74 (0.11) in the latanoprost group, and 0.86 (0.12) in the travoprost group ($P = 0.692$). There

Table 1. Baseline Characteristics of Enrolled Patients

	Bimatoprost (N = 35)	*Latanoprost (N = 38)*	*Travoprost with sofZia (N = 33)*	*Among-group P value*
Mean age (SD) in years	69.3 (12)	67.3 (10)	65.4 (12.6)	0.398
Sex, *n* (%)				
Male	13 (37.1)	19 (50.0)	13 (39.4)	0.493
Female	22 (62.9)	19 (50.0)	20 (60.6)	
Race, *n* (%)				
Caucasian	23 (65.7)	23 (60.5)	18 (54.5)	0.468
Black	6 (17.1)	7 (18.4)	9 (27.3)	
Hispanic	6 (17.1)	8 (21.1)	6 (18.2)	
Iris color, *n* (%)				
Brown	20 (57.1)	23 (60.5)	18 (54.5)	0.877
Blue	11 (31.4)	10 (26.3)	5 (15.2)	
Hazel	1 (2.9)	2 (5.3)	6 (18.2)	
Green	3 (8.6)	1 (2.6)	2 (6.1)	
Not available	—	2 (5.3)	2 (6.1)	
Diagnosis, *n* (%)				
Open-angle glaucoma	28 (80.0)	35 (92.1)	28 (84.8)	0.327
Ocular hypertension	7 (20.0)	3 (7.9)	5 (15.2)	
Treatment history[a], *n* (%)				
<1 year	3 (8.6)	6 (15.8)	7 (21.2)	0.790
1–3 years	9 (25.7)	8 (21.1)	10 (30.3)	
>3–5 years	5 (14.3)	6 (15.8)	6 (18.2)	
>5 years	12 (34.3)	13 (34.2)	7 (21.2)	
Not available	6 (17.1)	5 (13.2)	3 (9.1)	

[a]Duration of exposure to 1 or more IOP-lowering medications before baseline.
Abbreviations: IOP, intraocular pressure; SD, standard deviation.

in mean conjunctival hyperemia scores at latanoprost-treated baseline or at any follow-up visit ($P \geq 0.340$, Fig. 1). At month 3, the mean (SEM) score was 0.80 (0.12) in the bimatoprost group, 0.74 (0.10) in the latanoprost group, and 0.98 (0.13) in the travoprost group ($P = 0.340$). There were also no significant differences among the treatment groups in the change from baseline conjunctival hyperemia scores at week 1, month 1, and month 3 ($P \geq 0.586$). At month 3, the mean (SEM) change from baseline conjunctival hyperemia scores was 0.05 (0.10) in the bimatoprost group, 0.06 (0.10) in the latanoprost group, and 0.07 (0.13) in the travoprost group ($P = 0.994$).



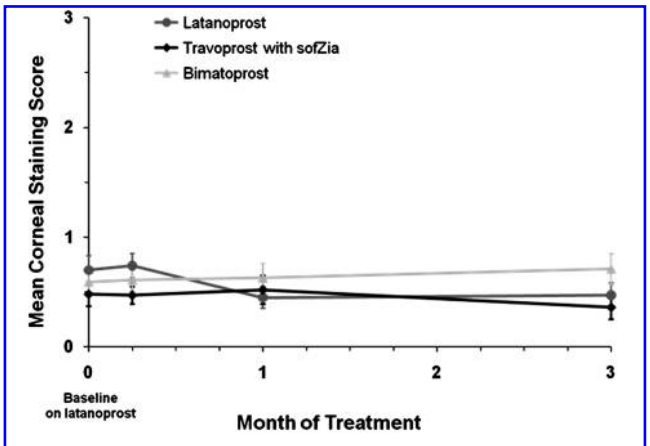
Visit	Mean Score (Standard Deviation) Bimatoprost (N = 35)	Latanoprost (N = 38)	Travoprost sofZia (N = 33)	Among-Group *P* Value
Baseline	0.74 (0.59)	0.74 (0.68)	0.86 (0.67)	0.692
Week 1	0.95 (0.74)	0.78 (0.74)	0.94 (0.86)	0.475
Month 1	0.83 (0.68)	0.78 (0.68)	0.98 (0.56)	0.443
Month 3	0.80 (0.68)	0.74 (0.57)	0.98 (0.73)	0.340

FIG. 1. Mean conjunctival hyperemia scores at each visit. There were no significant among-group differences in the mean hyperemia scores or in the mean change from baseline hyperemia scores at any visit ($P \geq 0.586$). Error bars represent

The baseline mean (SEM) corneal staining score was 0.59 (0.12) in the bimatoprost group, 0.70 (0.13) in the latanoprost group, and 0.48 (0.11) in the travoprost group ($P = 0.423$). There were no significant differences among the treatment groups in the baseline mean corneal staining score or the mean corneal staining score during follow-up ($P \geq 0.110$, Fig. 2). The mean change from baseline corneal staining scores was also similar among the treatment groups at week 1, month 1, and month 3 ($P \geq 0.083$). At month 3, the mean (SEM) change from baseline corneal staining scores was 0.15 (0.15) in the bimatoprost group, −0.18 (0.11) in the latanoprost group, and −0.07 (0.12) in the travoprost group ($P = 0.175$).

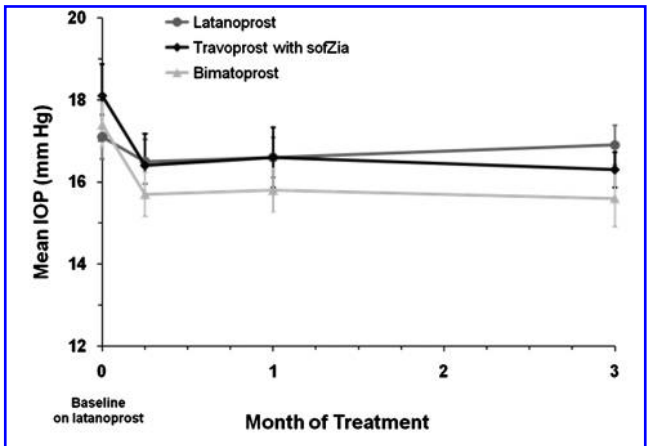
The baseline mean (SEM) TBUT was 9.1 (1.0) s in the bimatoprost group, 8.6 (0.8) s in the latanoprost group, and 7.9 (0.8) s in the travoprost group ($P = 0.578$). There were no significant differences among the treatment groups in the baseline mean TBUT or the mean TBUT at any follow-up visit ($P \geq 0.276$, Fig. 3). Similarly, there were no significant among-group differences in the mean change from baseline TBUT at week 1, month 1, or month 3 ($P \geq 0.546$). At month 3, the mean (SEM) change from baseline TBUT was 0.5 (0.9) s in the bimatoprost group, 0.4 (1.0) s in the latanoprost group, and 1.7 (0.8) s in the travoprost group ($P = 0.546$).

In this study, IOP measurements were taken at each visit as a safety precaution to ensure that IOP control was adequate. At latanoprost-treated baseline, the mean (SEM) IOP was 17.4 (0.5) mm Hg in the bimatoprost group, 17.1 (0.5) mm Hg in the latanoprost group, and 18.1 (0.8) mm Hg in



Visit	Mean Score (Standard Deviation)			
	Bimatoprost (N = 35)	Latanoprost (N = 38)	Travoprost sofZia (N = 33)	Among-Group *P* Value
Baseline	0.59 (0.72)	0.70 (0.79)	0.48 (0.65)	0.423
Week 1	0.61 (0.59)	0.74 (0.70)	0.47 (0.48)	0.342
Month 1	0.63 (0.73)	0.45 (0.61)	0.52 (0.74)	0.563
Month 3	0.71 (0.78)	0.47 (0.64)	0.36 (0.62)	0.110

FIG. 2. Mean scores of corneal staining with fluorescein at each visit. There were no significant among-group differences in the mean corneal staining scores or in the mean change from baseline corneal staining scores at any visit ($P \geq 0.083$). Error bars represent standard error of the mean.

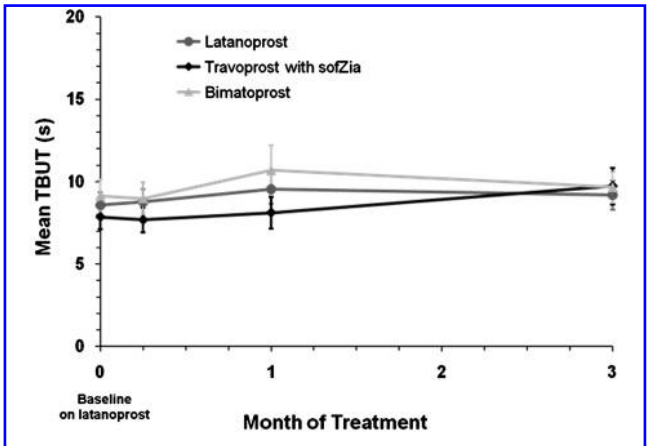


Visit	Mean IOP (Standard Deviation), mm Hg			
	Bimatoprost (N = 35)	Latanoprost (N = 38)	Travoprost sofZia (N = 33)	Among-Group *P* Value
Baseline	17.4 (3.2)	17.1 (3.3)	18.1 (4.4)	0.449
Week 1	15.7 (3.2)	16.5 (3.3)	16.4 (4.4)	0.516
Month 1	15.8 (3.0)	16.6 (3.0)	16.6 (4.2)	0.555
Month 3	15.6 (3.9)	16.9 (2.9)	16.3 (2.4)	0.207

FIG. 4. Mean intraocular pressure (IOP) at each visit. The among-group differences in the mean change in IOP from baseline were statistically significant at week 1, month 1, and month 3 ($P \leq 0.015$). Error bars represent standard error of the mean.

difference among the treatment groups in the mean IOP at baseline or at any follow-up visit ($P \geq 0.207$, Fig. 4). At month 3, the mean (SEM) IOP was 15.6 (0.7) mm Hg in bimatoprost group, 16.9 (0.5) mm Hg in latanoprost group, and 16.3 (0.4) mm Hg in travoprost group ($P = 0.207$). However, at each follow-up visit (week 1, month 1, and month 3), there was a significant among-group difference in the mean change in IOP from baseline ($P \leq 0.015$). At month 3, the mean (SEM) change from latanoprost-treated baseline IOP was −1.8 (0.6) mm Hg in the bimatoprost group, +0.2 (0.5) in the latanoprost group, and −1.7 (0.6) mm Hg in the travoprost group.

There were no serious adverse events during the study. Ocular adverse events were reported in 4 patients in each group (swollen eyelids, scratchiness, redness/scratchiness, and subconjunctival hemorrhage in the bimatoprost group; redness, flashes/floaters, photophobia, and dimmed vision in the latanoprost group; and redness/dryness/grittiness, scratchiness, dryness/scratchiness, and itchiness in the travoprost group).



Visit	Mean TBUT (Standard Deviation), seconds			
	Bimatoprost (N = 35)	Latanoprost (N = 38)	Travoprost sofZia (N = 33)	Among-Group *P* Value
Baseline	9.1 (5.8)	8.6 (4.8)	7.9 (4.4)	0.578
Week 1	9.0 (5.8)	8.8 (4.8)	7.7 (4.3)	0.585
Month 1	10.7 (8.3)	9.5 (5.4)	8.1 (5.5)	0.276
Month 3	9.7 (5.3)	9.2 (5.3)	9.7 (6.3)	0.909

FIG. 3. Mean tear breakup time (TBUT) at each visit. There were no significant among-group differences in the mean TBUT or in the mean change from baseline TBUT at any visit

Discussion

In this study, patients treated with latanoprost were randomized to topical treatment with bimatoprost, travoprost, or continuation on their existing therapy. The study treatments differed not only in the active drug but also in the type and concentration of preservative used. At 3 months, no significant differences among the PGAs were evident in objective clinical measures of ocular surface toxicity including conjunctival hyperemia, corneal staining, or TBUT despite differences in BAK concentration or in the preservative.

Although bimatoprost and travoprost are associated with an increased incidence of conjunctival hyperemia compared with latanoprost in treatment-naïve patients and in those patients treated after washout of previous medication,[17–19] no difference in mean conjunctival hyperemia scores was seen among the treatment groups in the present study. This finding may be explained by the study design in which patients were switched directly from latanoprost treatment to study treatment. A low

has been seen in a previous study in which patients replaced latanoprost with bimatoprost or travoprost.[20]

Previous studies have suggested that chronic treatment with topical ocular hypotensive medications may cause changes in the tear film and the conjunctival and corneal epithelium.[21,22] The clinical significance of these findings and the extent to which the active drug, rather than the preservative, may produce these effects have not been determined.[22,23] Studies in rabbits have shown deleterious effects of BAK on the ocular surface,[7,10–14] but findings in this animal model may not reflect the clinical situation. The accumulation of BAK in the conjunctiva that has been demonstrated in rabbits[15] has not been demonstrated in human eyes. Rabbit eyes differ from human eyes in key characteristics that are likely to affect the exposure of the ocular surface to preservative, such as a much slower blink rate (4–5 times/h vs. 6–15 times/min) and the presence of a nictitating membrane that could serve as a drug reservoir.[24] The inflammatory infiltration observed in the conjunctival epithelium of rabbit eyes exposed to BAK or BAK-containing medication[12] is not seen in human eyes treated with bimatoprost 0.03% containing 0.005% BAK.[2] Further, although changes in corneal epithelial cell morphology have been observed with latanoprost (0.02% BAK) in rabbits after only 3 min of exposure,[11] the long-term clinical use of latanoprost has been associated with a favorable profile in terms of both safety and ocular surface health.[25,26]

There have been few reports of the effects of BAK in human eyes. Corneal epithelium exposure to BAK was shown to be transient after instillation of BAK-containing drops, with BAK concentrations below the level of detection in the tear film at 5 min postinstillation in subjects who received a total of 5 drops of medication (BAK concentrations after chronic dosing could differ).[27] A single drop of a BAK-preserved β-blocker has been shown to decrease tear film stability in human subjects.[28] While a recent cross-sectional study of 101 patients demonstrated an increase in lissamine green staining with each additional BAK-containing medication, no relationship was identified between the number of BAK-containing medications and TBUT or Schirmer testing.[29] Although use of multidose bottles of ophthalmic medications is invariably associated with exposure to preservative, the potential effects of preservatives other than BAK, in particular sofZia, on the tear film and dry eye have not been well studied.

Studies in rabbits have suggested that travoprost with sofZia causes less corneal epithelial damage, conjunctival inflammation, and loss of conjunctival goblet cells compared with latanoprost preserved with BAK,[13,14] yet controlled clinical comparison studies to date have provided no evidence that travoprost preserved with sofZia is any better tolerated than travoprost preserved with BAK.[30,31] In the phase 3 clinical trial, no statistical differences were observed in either ocular hyperemia or discontinuations due to treatment-related adverse events between travoprost preserved with BAK and travoprost preserved with sofZia.[31] These results suggest that use of the preservative sofZia does not confer any advantage in short-term ocular tolerability over use of BAK. In a recent case series, patients who were using latanoprost and had symptoms of dry eye experienced significant improvement in TBUT and corneal staining after being switched to travoprost preserved with sofZia.[32] The study was not controlled, and it is possible that the improvement was due to the switch study design and regression to the mean, or by use of travoprost rather than latanoprost. However, it is also possible that preservative effects on ocular tolerability differ in patients with dry eye. Our study did not select for patients with dry eye symptoms, but patients with dry eye were not excluded, and no significant differences in tolerability were seen among the PGAs preserved with sofZia or varying concentrations of BAK over 3 months.

IOP was measured in this study to ensure that patients had adequate IOP control. A substantial mean decrease in IOP from latanoprost-treated baseline to month 3 was seen in both the bimatoprost and travoprost groups but not in the latanoprost group. In this study, however, IOP was considered a safety measure and was assessed at only 1 time of day at each visit.

In this study there was no advantage in ocular surface effects of travoprost preserved with sofZia over either latanoprost or bimatoprost, 2 PGAs preserved with BAK. The limitations of this study include its relatively short duration of 3 months and the lack of an a priori power calculation to determine sample sizes. Also, patients were not masked to treatment, and patients' history of exposure to latanoprost, specifically, and to other BAK-containing medications was not evaluated. If ocular surface effects of preservative are reversible, but 4 weeks of washout is inadequate to allow for ocular surface recovery, differences among the treatment groups in use of adjunctive medication containing BAK before washout could have affected the results. This seems unlikely, however, because there were no significant differences among the treatment groups in clinical characteristics of the study eyes at baseline, or in history of exposure to topical IOP-lowering medications. Although the study treatments had no significant effect on tear film stability or ocular surface damage over 3 months, their long-term effects, as well as their effects in patients taking multiple topical medications and in patients with severe ocular surface disease, require further investigation.

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Author Disclosure Statement

Jess T. Whitson, William B. Trattler, and Cynthia Matossian declare no proprietary interests in the study. Jess T. Whitson is a consultant of Alcon and is on the speaker's bureau of Alcon, Allergan, and Pfizer. William B. Trattler, a consultant of Alcon, Allergan, and Aton, has received research support from Allergan, and is on the speaker's bureau of Allergan. Cynthia Matossian is a consultant of AMO and has received lecture fees from Alcon, Allergan, and Ista. Julia Williams and David A. Hollander are employees of Allergan.

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