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CLINICAL INVESTIGATION

Effects of Switching to SofZia-Preserved Travoprost in Patients Who Presented with Superficial Punctate Keratopathy While Under Treatment with Latanoprost

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Abstract

Purpose: To investigate the effects of switching to SofZia-preserved travoprost (TRV) on superficial punctate keratopathy (SPK) observed in patients using benzalkonium chloride (BAC)-preserved latanoprost (LAT).

Methods: Patients with either primary open-angle glaucoma or ocular hypertension treated with LAT for at least 1 month who presented with SPK participated in this prospective, multicenter, open-label uncontrolled study. After the switch from LAT to TRV, patients were monitored at 2 weeks and at 1, 2, and 3 months. The use of concomitantly employed ophthalmic solutions was continued during the observation period. The intensity of SPK in each of five areas defined on the cornea was scored on a standard scale. Repeated measurements were tested with a linear mixed model.

Results: Of the 48 patients enrolled, 45 patients completed the study. After the switch to TRV, the mean SPK score in the whole cornea decreased significantly at every observation point ($P < 0.0001$ at each point) while intraocular pressure did not change significantly. Throughout the observation period, the SPK score tended to be higher in patients using a larger number of concomitant medications that contained BAC.

Conclusion: Switching to TRV improved SPK observed in a population using LAT, likely because of a decrease in exposure to BAC. **Jpn J Ophthalmol** 2010;54:7–14 © Japanese Ophthalmological Society 2010

Keywords: benzalkonium chloride, latanoprost, SofZia, superficial punctate keratopathy, travoprost

Introduction

Benzalkonium chloride (BAC), a quaternary ammonium compound, is a surfactant used as a preservative in many ophthalmic solutions, but it can cause adverse effects.[1,2] Adverse events involving the ocular surface include toxicity to epithelial cells and subclinical inflammatory changes in the conjunctiva and cornea, reduced tear film stability, and increased corneal permeability. If BAC is contained in ocular hypotensive agents, these unfavorable effects may worsen the tolerability of ophthalmic solutions.[1] Moreover, long-term exposure to BAC can reduce the success rate of glaucoma filtration surgery.[1]

Latanoprost (Xalatan eye drops, Pfizer Japan, Tokyo, Japan), a prostaglandin analog widely used in the treatment of glaucoma, contains 0.02% BAC as a preservative. In an open-label, multicenter study[3] of 158 patients conducted

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in Japan to evaluate long-term treatment with latanoprost, superficial punctate keratopathy (SPK) was observed as an adverse event in 15.2% of the patients. If that SPK was due to BAC, improvements in SPK could be expected after switching to a BAC-free solution. While there is no commercially available BAC-free latanoprost at present, travoprost preserved with SofZia (TRAVATANZ ophthalmic solution 0.004%, Alcon Japan, Tokyo, Japan), a non-BAC-preserved prostaglandin analog,[4,5] can be used clinically. SofZia (Alcon Laboratories, Fort Worth, TX, USA) is a proprietary ionic buffer system comprised of zinc, borate, and sorbitol that does not contain BAC.[4,5] Basic experiments in animals and cultured cells have revealed that travoprost preserved with SofZia is less cytotoxic than prostaglandin analogs preserved with BAC.[4,6,7] However, up to the time of preparation of this report, there were no studies on the effects of switching to SofZia-preserved travoprost on SPK observed in patients under treatment with latanoprost. In this study, the ophthalmic solution was switched to SofZia-preserved travoprost in patients who presented with SPK while under treatment with latanoprost and possible improvements in their SPK were studied.

Subjects and Methods

Subjects

Potential subjects of this study were patients with primary open-angle glaucoma or ocular hypertension treated either with latanoprost alone or in combination with other ophthalmic solutions for at least 1 month, in whom SPK was observed and who were judged by their physician to require a change in their ophthalmic solution to SofZia-preserved travoprost. The inclusion criteria were as follows: age ≥ 20 years; Humphrey Field Analyzer (program 30–2) mean deviation ≥ –15 dB; and continued use of all concomitant ophthalmic solutions after switching to SofZia-preserved travoprost, if used at the time of study participation. Exclusion criteria included current use of steroidal eye drops; complications with uveitis or scleritis; ocular injury within the 6 months previous to enrollment; intraocular surgery within the previous 3 months; ocular laser surgery within the previous month; current contact lens use; patients in whom applanation tonometry was difficult; and patients judged inappropriate for this study by their physician. Patients were recruited at the following four institutions: Nihonmatsu Eye Hospital, Nakano General Hospital, Ueno Eye Clinic, and Yoshikawa Eye Clinic.

Procedures

The inclusion period was from February to May 2008. The study was designed as a prospective, multicenter, open-label, uncontrolled study. Among the potential subjects who met the inclusion criteria but not the exclusion criteria, only those who signed the informed consent agreement approved by the Institutional Review Board of Meiwa Hospital were entered into the study after receiving a full explanation of the advantages and disadvantages of the switch in medication.

Participants visited their clinic at the time of switching from latanoprost to SofZia-preserved travoprost (baseline) and at 2 weeks and 1, 2, and 3 months thereafter. At each observation point they were examined by the same physician. Assessment of SPK by slit-lamp biomicroscopy, Goldmann applanation tonometry, photography of the anterior ocular segment, monitoring for adverse events, and checking of treatment adherence were performed at each observation point. Decimal visual acuity was measured at baseline and at 1 and 3 months during the observation period.

The ocular surface was stained with fluorescein using Fluores Test Paper (Showa Yakuhin Kako, Tokyo, Japan) soaked in saline solution, and SPK was observed through the cobalt blue filter of the slit-lamp biomicroscope. SPK was rated before, but not after, tonometry and perimetry at each observation point. The severity of SPK was scored according to the following system: 0 = no punctate staining; 1 = sparse punctate staining; 2 = dense punctate staining; 3 = coalesced, patchy staining; and 4 = coalesced, planar staining. Figure 1 shows the photograph used as the standard. The corneal surface was divided into five areas (Fig. 2): central, superior, nasal, temporal, and inferior, according to the report of the National Eye Institute/Industry Workshop,[8] and SPK in each area was scored. The score of the most intense staining observed in a given area was used as the score for the whole area.

Tear meniscus and tear secretion volume were measured at one of the observation points. To measure the tear meniscus, the tear was stained with fluorescein, and the height at the inferior eyelid margin was examined through the cobalt blue filter of the slit-lamp biomicroscope and assessed using a four-grade scale: not observed, linear, narrow, and sufficient. Tear secretion volume was measured by the one-minute Schirmer test reported by Bawazeer and Hodge:[9] topical anesthetic was applied to the eye, a Schirmer test strip (Color Bar Schirmer Tear Test, Eagle Vision, Memphis, TN, USA) was placed on the inferior eyelid, and the extent of wetting was measured in millimeters after 1 min.

At each visit, patients were asked whether they had experienced irritation, itching, or foreign body sensation, and whether they had noticed hyperemia, all of which are the potential adverse events associated with instillation of either latanoprost or SofZia-preserved travoprost. If patients experienced other subjective or objective adverse events, these were recorded individually.

At each observation point after switching to SofZia-preserved travoprost, patients were evaluated by the same physician, who was blind to the previous data of each patient. Therefore, data obtained at each observation point were recorded on a separate case card. After data were recorded, each case card was sent to the data collection facility (Yamazaki Eye Clinic).

Data Analyses

Data analyses were performed at the data collection facility and not at the institutions that recruited the patients. One eye of each patient was included in the analyses. If both eyes were eligible, the eye with the more severe SPK was chosen. JMP (Version 7.0.2, SAS Institute, Cary, NC, USA) was used for all analyses. SPK scores were analyzed as a continuous variable. In addition to the score of each area, the mean score of the five areas was used as a measure of the severity of SPK in the entire cornea. In order to evaluate whether the observation point had an effect, SPK scores, intraocular pressure, and visual acuity were analyzed using a linear mixed model and the restricted maximum likelihood (REML) method.[10] Besides observation points, corneal areas and other clinical factors were simultaneously included in the model, if necessary, to examine their effect on SPK scores. Contrasts[10] were used to test the significance of the differences between the levels of factors that were significant in the linear mixed model. Linear mixed models using the REML method are commonly used in analyses of longitudinal clinical data.[11,12] They are suited for analysis of data sets with repeated measurements in the same subject, when the number of measurements differs among the subjects because of missing values. Decimal visual acuity data were analyzed after logarithmic transformation. The McNemar test was used to test the difference between paired proportions.

Results

The study was conducted from February to August 2008. Forty-eight patients participated in the study. However, three patients withdrew from the study, and the remaining 45 (93.8%) patients were included in the analyses. Of the patients analyzed, two could not visit the clinic at 2 weeks and another two could not visit at 1 month. Therefore, 43 were evaluated at 2 weeks and at 1 month, and 45 at the other observation points. All 45 patients showed good adherence to treatment after switching to SofZia-preserved travoprost. Table 1 shows the demographics of the patients. The results of the one-minute Schirmer test showed that approximately 70% of the eyes evaluated in

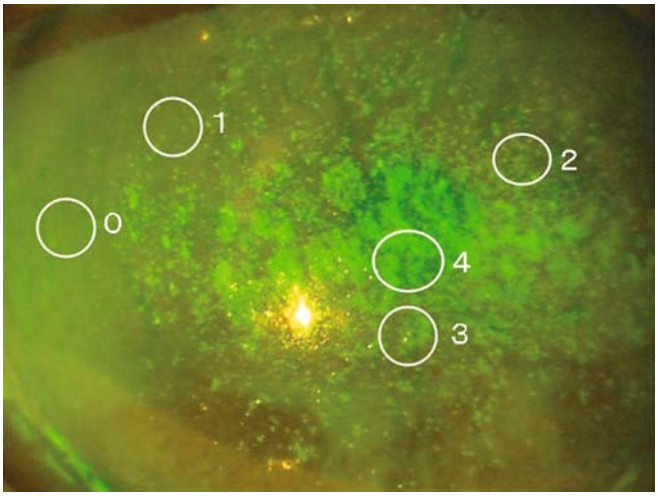

Figure 1. Photograph used as standard for scoring of superficial punctate keratopathy (SPK). The *number* beside each *circle* in the figure indicates the SPK score of that circle.

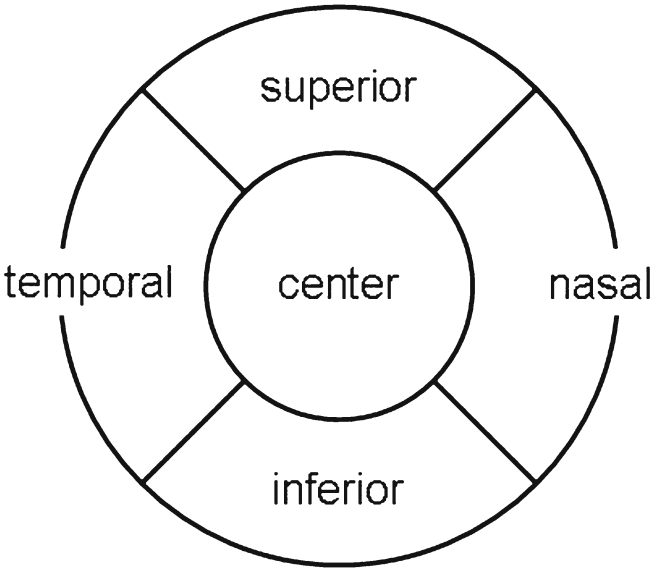

Figure 2. Diagram of the division of the corneal surface. This diagram is for the right eye. Its mirror image was used for the left eye.

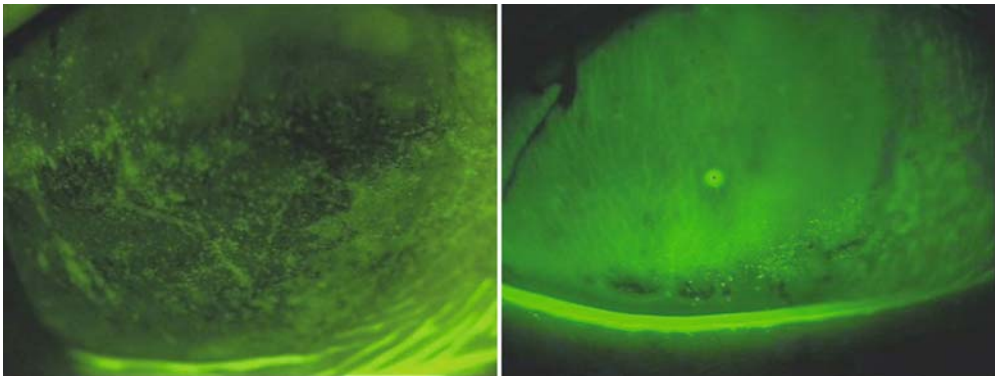

Figure 3. Photographs of the cornea of a patient who showed improvement of SPK after switching the ophthalmic solution: the mean SPK score in the entire cornea was 2.4 at baseline (*left*) and 0.6 at 2 weeks (*right*). SPK scores continued to be low for this patient.

Table 1. Demographics of the patients

	Mean ± SD (range), *n* (%), or range (median), *n* = 45
Age (years)	68.4 ± 9.2 (44–88)
Sex	
Male	15 (33.3%)
Female	30 (66.7%)
Diagnosis	
Ocular hypertension	1 (2.2%)
Primary open-angle glaucoma	21 (46.7%)
Normal tension glaucoma	23 (51.1%)
Mean deviation (Humphrey, Central 30-2, dB)	–6.12 ± 4.92 (–14.82 to 2.39)
Best-corrected visual acuity	0.6 to 1.5 (1.2)
Ocular surface complications	
Conjunctivochalasis	4 (8.9%)
Pingueculitis	2 (4.4%)
Pterygium	1 (2.2%)
Keratoconjunctivitis sicca	1 (2.2%)
One-minute Schirmer test results[a]	
Severe dry eye (≤2 mm)	23 (52.3%)
Mild to moderate dry eye (3 to 6 mm)	8 (18.2%)
≥7 mm	13 (29.5%)
Tear meniscus grade	
Not observed	0 (0%)
Narrow	15 (33.3%)
Linear	21 (46.7%)
Sufficient	9 (20.0%)
Number of ophthalmic solutions concurrently used with latanoprost/travoprost	
All types	1.3 ± 1.0 (1 to 4)
Only preparations containing BAC	1.2 ± 0.9 (1 to 3)

BAC, benzalkonium chloride.
[a]Values and percentages are for 44 patients (one patient's data were incomplete).

this study showed severe or moderate dryness following the definition of Bawazeer and Hodge.[9] The ophthalmic solutions used in combination with latanoprost and those used with SofZia-preserved travoprost included the following ocular hypotensive agents: β-adrenergic receptor antagonists, α-adrenergic receptor antagonists, and carbonic anhydrase inhibitors; and the following solutions other than ocular hypotensive agents: olopatadine hydrochloride, pirenoxine, sodium hyaluronate, and artificial tears. All except one β-adrenergic receptor antagonist contained BAC.

Changes in SPK scores in each corneal area are shown in Table 2. The linear mixed model analysis revealed that corneal areas and observation points had a statistically significant effect on SPK scores (observation points, $P < 0.0001$; corneal areas, $P < 0.0001$). A contrast test revealed that at each observation point SPK scores decreased significantly in all corneal areas except the superior area compared to baseline (Table 2). SPK scores differed among corneal areas during the entire study period; a contrast test revealed that the score was highest in the inferior area and lowest in the superior area (inferior > nasal, $P < 0.0001$; nasal > central, $P = 0.037$; central > temporal, $P = 0.0028$; temporal > superior, $P < 0.0001$).

The mean SPK score in the entire cornea (mean ± SD) was 1.4 ± 0.6 at baseline, 0.7 ± 0.5 at 2 weeks, 0.6 ± 0.4 at 1 month, 0.7 ± 0.6 at 2 months, and 0.7 ± 0.5 at 3 months. Similar to the results of the analysis of each corneal area, the linear mixed model analysis revealed that the effect of observation points on the mean SPK score in the entire cornea was significant ($P < 0.0001$). Furthermore, a contrast test revealed that at every observation point the mean SPK score in the entire cornea was significantly decreased compared to baseline (2 weeks, $P < 0.0001$; 1 month, $P < 0.0001$; 2 months, $P < 0.0001$; 3 months, $P < 0.0001$). Figure 3 shows an example of the anterior ocular segment that showed improvement of SPK after switching the ophthalmic solution.

Changes in the mean SPK score in the entire cornea were analyzed in relation to the number of ophthalmic solutions used concomitantly with either latanoprost or SofZia-preserved travoprost using the linear mixed model. The number of concomitant ophthalmic solutions, as well as observation points, significantly affected the mean SPK score (observation point, $P < 0.0001$; number of concomitant ophthalmic solutions, $P = 0.02$), showing that the larger the number of concomitant ophthalmic solutions, the higher the SPK score tended to be during the entire observation period (Fig. 4). Similar results were obtained regarding the number of ophthalmic solutions containing BAC: the number of concomitant ophthalmic solutions containing BAC, as well as observation point, significantly influenced the mean SPK score (observation point, $P < 0.0001$; number of concomitant ophthalmic solutions containing BAC, $P = 0.021$). In addition, a contrast test revealed that the larger the number of BAC-containing solutions used concomi-

Table 2. Changes in SPK scores in each area of the cornea

Area of the cornea	Observation point									
	Baseline (n = 45)	2 weeks (n = 43)		1 month (n = 45)		2 months (n = 43)		3 months (n = 45)	
	Mean ± SD	Mean ± SD	P value compared to baseline	Mean ± SD	P value compared to baseline	Mean ± SD	P value compared to baseline	Mean ± SD	P value compared to baseline
Superior	0.3 ± 0.5	0.1 ± 0.3	0.1128	0.1 ± 0.4	0.2149	0.2 ± 0.5	0.3914	0.2 ± 0.4	0.1128
Temporal	1.1 ± 1.0	0.5 ± 0.7	<0.0001	0.3 ± 0.6	<0.0001	0.4 ± 0.6	<0.0001	0.5 ± 0.7	<0.0001
Central	1.6 ± 0.8	0.7 ± 0.7	<0.0001	0.5 ± 0.6	<0.0001	0.4 ± 0.6	<0.0001	0.6 ± 0.7	<0.0001
Nasal	1.6 ± 1.1	0.8 ± 0.7	<0.0001	0.7 ± 0.9	<0.0001	0.8 ± 1.1	<0.0001	0.6 ± 0.9	<0.0001
Inferior	2.5 ± 1.1	1.5 ± 1.1	<0.0001	1.5 ± 0.9	<0.0001	1.4 ± 1.2	<0.0001	1.5 ± 1.1	<0.0001

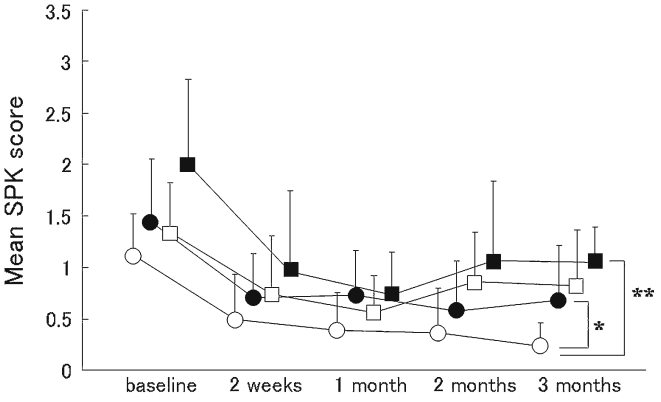

Figure 4. Changes in SPK scores in relation to the number of concomitantly used ophthalmic solutions. *Symbols* and *vertical bars* show the mean ± SD. Each symbol represents the number of ophthalmic solutions used concomitantly either with latanoprost or travoprost: ○, none (n = 10); ●, one (n = 19); □, two (n = 10); ■, three to four (n = 6). *The difference in SPK scores across the entire study period between the group using one solution and the group using none (P = 0.0422, contrast analysis). **The difference in the SPK scores across the entire study period between the group using three to four solutions and the group using none (P = 0.0024, contrast analysis). The SPK scores decreased significantly in each group at 2 weeks or later compared with the baseline (P < 0.0001 at 2 weeks, P < 0.0001 at 1 month, P < 0.0001 at 2 months, P < 0.0001 at 3 months in each group).

tantly with latanoprost or SofZia-preserved travoprost, the higher the SPK score during the entire observation period tended to be (group using none < group using one, P = 0.0469; group using none < group using two to three, P = 0.0059).

Changes in the mean SPK score in the entire cornea were also analyzed using a linear mixed model including the one-minute Schirmer test value and the tear meniscus grade. Neither of these factors had a significant effect on the SPK scores (one-minute Schirmer test value, P = 0.1855; tear meniscus grade, P = 0.7211). Likewise, no other clinical factors showed a significant effect on the SPK score by a linear mixed model (age, P = 0.1055; sex, P = 0.6659; type of glaucoma, P = 0.9088; type of ocular surface complication, P = 0.3298).

The changes in intraocular pressure and visual acuity were also analyzed separately using the linear mixed model. Intraocular pressure (mean ± SD) was 14.1 ± 3.0 (n = 45) at baseline, 13.4 ± 3.2 (n = 43) at 2 weeks, 13.6 ± 3.3 (n = 45) at 1 month, 13.8 ± 3.0 (n = 43) at 2 months, and 13.5 ± 2.5 (n = 45) at 3 months, showing no significant changes at any observation point after the ophthalmic solution was switched (P = 0.1852). Visual acuity ranged from 0.6 to 1.5 (median 1.2) at baseline versus from 0.5 to 1.2 (median 1.2) at 1 month and from 0.4 to 1.2 (median 1.2) at 3 months, showing no significant changes at any observation point either (P = 0.0942).

The number of patients who experienced irritation, itching, or foreign body sensation or who noted hyperemia at baseline was compared with the number who experienced an adverse event at one or more observation points after switching the ophthalmic solution (Table 3). The fre-

Table 3. Adverse events before and after switching the ophthalmic solution

Adverse events	Number of patients who complained of adverse events (n = 45)		
	Baseline (latanoprost)	After switching to SofZia-preserved travoprost[a]	P value (McNemar test)
Irritation	7 (15.6)	11 (24.4)	0.2059
Itching	5 (11.1)	8 (17.8)	0.2568
Foreign body sensation	12 (26.7)	6 (13.3)	0.0339
Awareness of hyperemia	10 (22.2)	15 (33.3)	0.1655

[a]Patients who experienced an event at one or more observation points are counted as one.

quency of foreign body sensation was significantly lower after the switch to SofZia-preserved travoprost. No serious adverse events were observed in any patient, including those who participated in the study but were not included in the analyses.

Discussion

In a multicenter study carried out in Japan to evaluate the efficacy and safety of latanoprost containing 0.02% BAC, SPK as an adverse event was reported in 15.2% of the patients.[3] In the present study, the ophthalmic solution was switched to SofZia-preserved travoprost in patients under treatment with latanoprost who presented with SPK. The results showed that SPK observed during treatment with latanoprost improved significantly after the switch to SofZia-preserved travoprost. This improvement was noted as early as 2 weeks after the medication was switched. Taking into consideration that the corneal epithelium is estimated to renew every 3.5–7 days,[13] it may be reasonable to infer that the improvement of SPK was noted at 2 weeks because factors causing epithelial disorders had been reduced by the switch of the ophthalmic solution. On the other hand, while BAC is the most common antimicrobial preservative used in ophthalmic solutions, it is known to cause several adverse effects on the ocular surface such as epithelial disorders.[1,2] Therefore, the decrease in the total dose of BAC as a result of switching the ophthalmic solution may have contributed to the improvement in SPK observed in this study. Previous experiments in animals and cultured cells have similarly shown that SofZia-preserved travoprost is less cytotoxic than latanoprost.[4,6,7]

The present results do not indicate whether switching to SofZia-preserved travoprost has an effect on the ocular surface in patients who do not develop SPK while under treatment with latanoprost. In addition, although SPK was rated at each observation point by observers masked to the patients' previous data, as this study was not conducted in a crossover manner or according to a randomized, placebo-controlled design, further research is needed to examine the universality of our results. Still, few studies have compared the effects of SofZia-preserved travoprost and BAC-preserved prostaglandin analogs on epithelial disorders in human eyes. Henry et al.[14] reported that when ophthalmic solutions were switched to SofZia-preserved travoprost in patients using either latanoprost or bimatoprost, both of which are preserved with BAC, the patients experienced improvement in subjective scores for ocular surface diseases. They also reported an improvement in the severity of objective hyperemia, but they did not examine epithelial disorders such as SPK. While our observation results are comparable to those of Henry et al.,[14] this is the first report showing objectively that epithelial disorders such as SPK can be improved in human eyes by switching from latanoprost to SofZia-preserved travoprost.

Although improvement of SPK was observed regardless of the use, or not, of concomitant ophthalmic solutions, the larger the number of concomitant ophthalmic solutions and the larger the number of concomitant ophthalmic solutions containing BAC, the higher the SPK score tended to be during the entire observation period. Moreover, our results showed that SPK occurred most commonly in the inferior areas, both before and after the ophthalmic solution was switched, in agreement with the view that SPK caused by drug toxicity tends to occur in the inferior corneal area.[15] These findings suggest that not only SPK observed under treatment with latanoprost but also SPK remaining after switching the drugs is likely due to the effect of BAC contained in the concomitantly used ophthalmic solutions. At the same time, our results may suggest a dose-dependent relationship between the BAC in all ophthalmic solutions and the frequency of SPK. Leung et al.[16] showed that in patients with glaucoma the frequency of abnormal results on the lissamine green staining test correlated with the number of BAC-containing ophthalmic solutions the patients used. Our results correspond well with their results. On the other hand, BAC is not a single chemical substance but a mixture of alkyldimethylbenzylammonium chlorides whose activity varies with the alkyl chain length.[1,17] Therefore, the exact composition of BAC may differ among ophthalmic solutions. Moreover, latanoprost contains 0.02% BAC, the highest concentration among the commercially available medications for glaucoma, which may make SPK more likely to occur. Detailed studies are needed to examine the relationship between differences in the concentration or composition of BAC and the likelihood of developing SPK.

Approximately 70% of the patients in this study were considered to have mild to moderate or more severe dry eye, which suggests that our patient population may be biased toward those with decreased tear volume compared with the general population. When tear volume is low, drugs are not diluted in the conjunctival sac, and as a result,

the ocular surface may be more susceptible to the effects of cytotoxic agents. Thus, patients in this study may have been more likely to develop SPK due to BAC-containing agents. On the other hand, our investigation did not reveal any relationship between the one-minute Schirmer test or tear meniscus grade and SPK, although it seems likely that SPK would be more severe with increasing dryness of the eyes. Meanwhile, it has been pointed out that the use of multiple ocular hypotensive agents can reduce tear volume and tear film stability.[18] Thus, as the type and number of concomitant ophthalmic solutions varied among the patients, it is possible that tear meniscus measurements in this study were not accurate enough to show the relationship with SPK severity. It may be necessary to reevaluate the relationship between the severity of dryness and the change in SPK following the switch of ophthalmic solutions in a study like this one, after some improvements are made to the evaluation methods to assess tear status.

Theoretically, the difference in cytotoxicity between latanoprost and travoprost as active ingredients should also be considered as a reason for improvement of SPK after switching from latanoprost to SofZia-preserved travoprost. However, Guenoun et al. showed that none of these drugs is cytotoxic[19] but rather they have a cytoprotective effect.[20] Therefore, factors other than preservatives may also have to be considered as responsible for the improvement in SPK after the medication was switched in this study, including potential superiority of the cytoprotective effect of travoprost over latanoprost. Further investigations are required to clarify this point.

Some reports state that the effects of latanoprost and travoprost on intraocular pressure are comparable,[21] and some that travoprost is superior to latanoprost.[22] Another study showed that the effect of travoprost on intraocular pressure is comparable whether BAC is present or not.[23] In our patients, intraocular pressure was slightly reduced after they switched from latanoprost to SofZia-preserved travoprost, but the difference was not statistically significant. This result is consistent with that of previous reports.

Regarding adverse events other than SPK, the frequency of foreign body sensation decreased after the switch to SofZia-preserved travoprost. This decrease may have occurred in response to the objective improvement of SPK. Adherence in our patients after switching was good, and there were no serious adverse events. However, Kumar et al.[24] systematically switched patients from latanoprost to BAC-preserved travoprost, but 4.3% of the patients were switched back to latanoprost due to intolerance. In the present study, improvement of SPK may have contributed to the absence of patients showing intolerance.

Miyata et al.[25] report a grading method to assess SPK based on the proportion of fluorescein-stained area relative to the total area of the cornea and the staining density. It is, however, difficult to assess findings in each area of the cornea with their method. We used a cornea diagram based on a report of the National Eye Institute/Industry Workshop.[8] We believe that our results show the usefulness of this diagram to assess SPK in each area of the cornea.

In summary, patients who presented with SPK under treatment with latanoprost showed a significant improvement in SPK without significant changes in intraocular pressure after the ophthalmic solution was switched to SofZia-preserved travoprost. Although further studies are needed to confirm the universality of our results, the absence of BAC in SofZia-preserved travoprost seemed to play a role in the improvement of SPK.

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