

Incidence of deepening of the upper eyelid sulcus on treatment with a tafluprost ophthalmic solution

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Abstract

Purpose Deepening of the upper eyelid sulcus (DUES), one symptom of prostaglandin-associated periorbitopathy, was recently found to be an additional side effect of prostaglandin-related ophthalmic solutions. Here, we prospectively investigated the incidence and factors associated with DUES in Japanese open-angle glaucoma patients initially treated with benzalkonium chloride (BAK)-preserved tafluprost (TAF).

Methods In this open-label prospective study instilling TAF in one eye, mean deviation (MD) and intraocular pressure (IOP) were measured, and facial photographs and subjective reports of DUES were obtained at intervals over 6 months. Three ophthalmologists independently assessed the photographs of DUES and reached consensus. Relationships between demographic and ocular/systemic factors (age, sex, MD, refraction and IOP reduction) and DUES occurrence were evaluated.

Results Forty-three eyes of 43 glaucoma patients (24 men and 19 women) were evaluated. Mean IOP before treatment was 16.6 ± 2.7 and after treatment, 14.1 ± 2.3 mmHg ($P < 0.001$). The objective rate of DUES was 9 % (4/43) at

2 months, 14 % (6/43) at 4 months and 14 % (6/43) at 6 months. During this period, only one patient self-reported an occurrence of DUES. No significant association was found between DUES occurrence and any of the demographic, ocular, or systemic factors.

Conclusions Physicians should inform patients about DUES as a minor side effect when prescribing TAF for IOP control.

Keywords Prostaglandin-associated periorbitopathy · Deepening of the upper eyelid sulcus · Prostaglandin analog · BAK-preserved tafluprost · Japanese

Introduction

Prostaglandin analogs (PGAs) are currently the preferred choice of treatment for glaucoma because they have a strong intraocular pressure (IOP)-lowering effect and can control circadian variations in IOP throughout the day without long-term drift or severe systemic side effects [1, 2]. However, PGAs do have apparent side effects on the eye and its immediate surroundings, including iris and lid pigmentation, increased eyelash growth, and conjunctival hyperemia [3]. Apart from these typical side effects, the most noticeable symptom of prostaglandin-associated periorbitopathy (PAP), deepening of the upper eyelid sulcus (DUES), has been reported after a decade of clinical PGA use. PAP is a recognized clinical entity that includes periorbital fat atrophy, DUES, ptosis, enophthalmos and dermatochalasis involution [4]. However, PAP has not been formally defined.

DUES was first reported by Peplinski and Albani Smith [5], with additional reports on bimatoprost (BIM) [6–8] and travoprost (TRV) published subsequently [9]. In a previous

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study, we found that 60 % of Japanese open-angle glaucoma (OAG) patients developed DUES 3 months after switching treatment from latanoprost (LAT) to BIM [10]. In another study, DUES occurred in approximately half of the patients (53 %) after 4 months of TRV treatment [11]. Regarding the first released and most widely used PGA, LAT, some reports describe DUES caused by long-term LAT use in a single eye [12, 13].

Benzalkonium chloride (BAK)-preserved TAF (Tapros[®] 0.0015 %; Santen, Tokyo, Japan) is a domestically produced anti-glaucoma eye drop containing a prostaglandin-F2 α (PGF2 α) analog derivative with high affinity for the prostaglandin F (FP) receptor because it contains fluorine [14]. TAF has an efficacy equivalent to LAT and TRV in reducing IOP in OAG patients [15, 16], and also has a significant IOP reduction effect in patients with normal-tension glaucoma (NTG) [17].

To date, TAF-induced DUES has been reported in only one retrospective study in which the upper eyelid sulcus was compared in glaucoma patients who used one of four PGAs (LAT, TRV, BIM, or TAF) in one eye [13]. The rate of DUES was 18 % for patients who used TAF; the lowest value among the above-described PGF2 α analogs. However, the duration of treatment for each PGA and facial differences between the upper eyelids before PGA treatment were not considered. Recently, a large randomized multicenter clinical trial of preservation-free TAF (Taflotan[®] 0.0015 %; Santen, and Zioptan, by Merck, Whitehouse Station, NJ, USA) and a large population-based study reports a significant IOP-lowering effect for TAF, although any adverse PAP events, including DUES, are unreported [18, 19]. However, it is not possible to say that there were no symptoms of PAP in these studies simply because there were no adverse events.

In the present study, we monitored the occurrence of DUES in patients using BAK-preserved TAF as an initial treatment. This was because DUES is the most prominent clinical feature of PAP and one of the most significant adverse cosmetic events associated with the condition (although ocular side effects may also develop). Additionally, we investigated local and systemic factors potentially related to the occurrence of DUES.

Subjects and methods

This was an open-label prospective study. All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent (including the use of photographs) was obtained from all patients for inclusion in the study. The study protocol was approved by

the Ethics Committee of the Miyata Eye Hospital (Miyazaki, Japan).

Forty-three consecutive Japanese patients who were initially diagnosed with OAG at the Yotsuya Shirato Eye Clinic (Tokyo, Japan) were enrolled in this study from November 2009 to September 2010. OAG was diagnosed according to the presence of glaucomatous optic nerve head damage with corresponding visual field damage, an unoccluded normal open angle, and lack of other ocular abnormalities or history of other ocular diseases. The exclusion criteria included the use of eye drops within the previous 12 months or the use of an oral agent such as acetazolamide, a previous history of intraocular surgery (including laser treatment), and the presence of other ocular diseases affecting the IOP.

The efficacy of initial glaucoma therapy is normally evaluated using a one-eye trial, with the exception of advanced or emergency cases [20, 21]. Using this approach, the rate of IOP reduction can be more accurately judged by taking into consideration diurnal or day-by-day variations in IOP. Briefly, after confirming the difference in IOP between both eyes, one eye was treated with a hypotensive eye drop while the second eye was observed as a control. When both eyes met the entry criteria, we initiated TAF medication in the eye showing greater mean deviation (MD), and the same medication was continued for 6 months. However, when medication became necessary in the control eye, we initiated TAF application there, too.

A single examiner measured IOP, checked the condition of the ocular surface and optic disc by slit lamp examination and took photographs every 2 months for up to 6 months (4 measurements were taken over the entire observation period, including the starting point). Facial photographs showing the eyebrow and lower eyelid with no tension in the frontalis muscle were taken using a 9.1 megapixel digital camera (EX-FC 100; Casio, Tokyo, Japan) without a flash and with the same settings (including camera-to-subject distance).

The mean IOPs following treatment with TAF (IOP_{TAF} ; three consecutive IOP measurements after starting TAF treatment, excluding the starting point) were retrieved from each patient's medical records. The change in IOP was calculated as $\Delta IOP = IOP_{TAF} - IOP_{base}$, where IOP_{base} is the mean IOP without medication (IOP_{base} ; 3 consecutive IOP measurements before starting TAF treatment). The IOP was measured using a Goldman applanation tonometer (Haag Streit, Koeniz, Switzerland), and a slit lamp microscopy examination was conducted at every outpatient visit at approximately the same time of day after applying one drop of topical oxybuprocaine hydrochloride anesthesia (0.4 % Benoxil[®], Santen). Additionally, the refraction was measured using an automatic refractor/keratometer (ARK-900; Nidek, Tokyo, Japan) during each visit.

Three ophthalmologists independently assessed the upper eyelid on the TAF-instillation side for each patient by evaluating a series of four photographs (at the starting point, and after 2, 4 and 6 months). The eye receiving TAF had been identified to the ophthalmologists prior to evaluation. The three photographs taken after starting TAF (2, 4, and 6 months) were displayed on a 21-in liquid-crystal display (FlexScan L997; Eizo, Tokyo, Japan) in that order and compared to the initial (starting point) photograph of the TAF-administered eye. When changes to the upper eyelid sulcus were recognized, the photograph was marked as positive, regardless of the degree of deepening in comparison with the initial photograph. When three observers concurred on the deepening of the palpebral in the same photograph, the patient was judged as DUES-positive. The observers stipulated the initiation of DUES as the date of the earliest DUES-positive photograph, confirmed in subsequent (2nd and 3rd) pictures. The patients were asked to self-assess changes in the deepening of the palpebral at each visit. This series of methods for appraising DUES was the same as applied previously, using the same camera and visualization process [10, 22].

All analyses were performed using JMP 9.0.2 statistical software (SAS Inc., Cary, NC, USA). Two-sided *P* values <0.05 were considered to indicate significance. The data are presented as mean ± SD.

Results

All 43 patients (43 eyes) completed the 6-month study without drop-outs or any severe ocular/systemic adverse effects. There were 37 eyes with NTG and six eyes with primary open angle glaucoma (POAG). Demographic data are presented in Table 1. No additional medications besides TAF were administered to either eye during the observation period.

IOP measurements

The mean IOP from three consecutive visits before (IOP_{base}) and after (IOP_{TAF}) starting TAF were 16.6 ± 2.7 and 14.1 ± 2.3 mmHg, respectively (ΔIOP = -2.5 mmHg, *P* < 0.001, paired *t* test).

Incidence of objective DUES

The objective incidence rate of DUES was 9 % (4/43) at 2 months, 14 % (6/43) at 4 months, and 14 % (6/43) at 6 months (Table 2). Six patients had NTG. All three ophthalmologists attained consensus on all judgments. Figure 1 shows the development of DUES in one patient (OS), which appeared 2 months after starting TAF.

Table 1 Background of Japanese glaucoma patients related to the eye treated with BAK-preserved tafuprost ophthalmic solution

Characteristic	Value
Age (years)	48.8 (10.8)
Number of patients	43
Sex	
Male	24
Female	19
Spherical equivalent refraction (D)	-5.7 (4.1)
Mean deviation (dB)	-6.5 (5.0)
Mean IOP over the last three visits ^a before treatment (mmHg)	16.6 (2.7)
Mean IOP over the first three visits ^b after starting treatment with TAF (mmHg)	14.1 (2.3) ^c

All data are numbers or mean (SD)

IOP intraocular pressure, TAF tafuprost ophthalmic solution

^a This represents the three consecutive IOP measurements up to and including the treatment starting point (IOP_{base})

^b This represents the three consecutive IOP measurements after the start of TAF application, excluding the starting point (IOP_{TAF})

^c *P* < 0.001, comparison analysis by paired *t* test between the IOP_{base} and IOP_{TAF}

Table 2 The change in objective DUES occurrence after starting BAK-preserved tafuprost ophthalmic solution

	Start	2 months	4 months	6 months
Objective signs				
DUES				
Positive	0/43 (0)	4/43 (9)	6/43 (14)	6/43 (14)
Negative	43/43 (100)	39/43 (91)	37/43 (86)	37/43 (86)

All data are given as the number of cases (%)

DUES deepening of the upper eyelid sulcus

Subjective symptoms

Of the objectively DUES-positive patients, at 2 months after starting TAF, one of four (25 %) was subjectively aware of DUES (Table 3). The same patient still reported DUES at 6 months, at which time two additional patients also had DUES, of which they were unaware. The final rate of subjective DUES-positive patients was 17 % (1/6) throughout the full observation period. None of the other objectively DUES-negative patients complained of the condition.

Factors related to the occurrence of DUES

When comparing the objectively DUES-positive (6/43) and DUES-negative (37/43) patients, there was no significant relationship between the presence of DUES and age (*P* = 0.159), sex (*P* = 0.758), MD (*P* = 0.484), refraction (*P* = 0.149), or IOP reduction (*P* = 0.303) (Table 4).

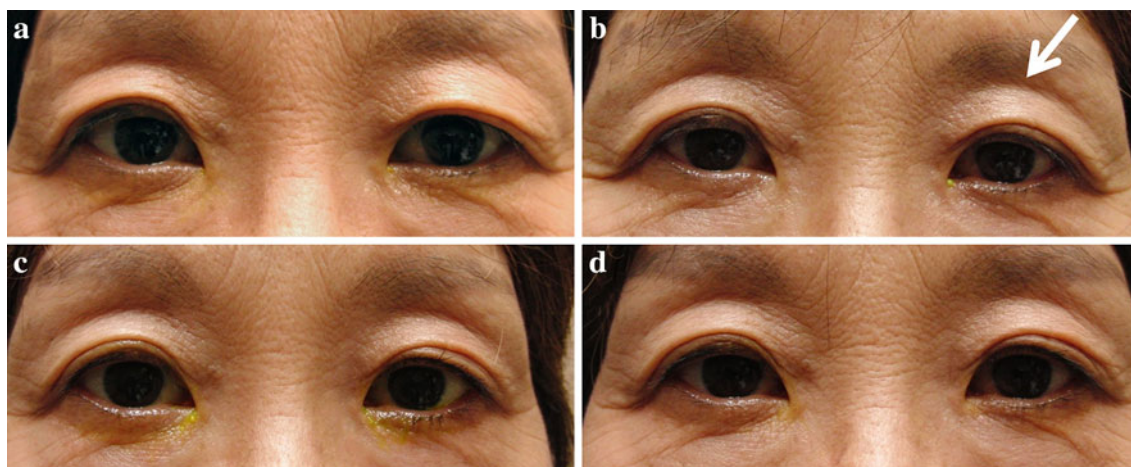


Fig. 1 A case of DUES caused by BAK-preserved tafluprost ophthalmic solution. This 59-year-old woman showed DUES OS 2 months after starting tafluprost ophthalmic solution (**b** white arrow). **a–d** 0 month (starting point), and 2, 4, and 6 months after starting tafluprost, respectively

Table 3 The change in subjectively reported DUES among objectively DUES-positive patients after starting BAK-preserved tafluprost ophthalmic solution

	Start	2 months	4 months	6 months
Subjective signs				
DUES				
Positive	0/0 (0)	1/4 (25)	1/6 (17)	1/6 (17)
Negative	0/0 (0)	3/4 (75)	5/6 (83)	5/6 (83)

All data are given as the number of cases (%)

DUES deepening of the upper eyelid sulcus

Table 4 Comparison of clinical factors affecting the incidence of DUES

	DUES-positive	DUES-negative	<i>P</i> value
Number of patients	6	37	–
Age (years)	53.3 (4.4)	48.1 (11.2)	0.16*
Sex (male/female)	3/3	21/16	0.76†
Mean deviation (dB)	–6.7 (5.0)	–5.1 (5.5)	0.48*
Refraction (D)	–3.8 (2.9)	–6.0 (4.2)	0.15*
IOP reduction by tafluprost (mmHg)	–1.8 (1.8)	–2.7 (1.6)	0.30*

All data are numbers or mean (SD)

DUES deepening of the upper eyelid sulcus, IOP intraocular pressure

* Paired *t* test

† Fisher's exact test

Discussion

This may be the first prospective study to investigate the incidence of DUES after starting TAF treatment. The

current information on ocular side effects of TAF is limited to a few studies [15, 18, 19]. Although we monitor patients for increased IOP, conjunctival hyperemia, and superficial punctate keratitis after prescribing TAF for IOP control, we should be aware of the possibility that we may be overlooking DUES as well as other possible symptoms of PAP.

In the present study, the rate of TAF-induced DUES was 9 % (4/43) at 2 months, 14 % (6/43) at 4 months, and subsequently remained the same. Recently, we demonstrated in a prospective manner the rate of BIM-induced DUES and its recovery using the same methodological conditions as in the present study [10, 22]. In one series of that trial, 60 % of patients who switched from LAT to BIM showed DUES at 6 months. However, a potential shortcoming regarding this result is that DUES may have already occurred after extended LAT use, although this was not noticed by either the observers or patients. Therefore, the rate of DUES with BIM might have been underestimated in the previous investigation. In another Japanese prospective study, TRV induced DUES in 53 % of subjects at 4 months [11]. Although the previous reports cannot be directly compared to the current study because of differences in patient populations as well as other related factors, TAF might induce much lower rates of DUES than BIM or TRV.

Similarly, in a retrospective investigation, DUES occurred most frequently after BIM usage (60 %), followed by TRV (50 %), LAT (24 %), and TAF (18 %) [13]. In that study, the rate of DUES was evaluated based on the difference between both upper eyelid sulci by comparing facial photographs of patients who used PGAs in a single eye. However, the rate of DUES among the four PGAs should not have been compared directly because the treatment duration and original differences between the upper eyelid sulci were not considered.

The reason for the different frequencies of DUES among PGAs is unclear. Our hypothesis is that DUES is dependent on the stimulation of the FP receptor in the orbital tissue, and that BIM may be the strongest stimulator among all PGAs. According to a basic research study, fat atrophy or the inhibition of adipocytes may play a role in DUES [23]. The lowest density of adipocytes obtained from preaponeurotic fat biopsies was from BIM-treated patients among subjects treated with BIM, TRA, or LAT. However, TAF was not investigated. The difference in action of each PGA on adipose cells may be one reason for the different phenotypic alterations. Additionally, the inhibition of adipocyte differentiation influences DUES through the activation of the FP receptor [24–26]. Stimulation of the EP3 receptor is also thought to inhibit adipocyte differentiation [27]. Differences in the affinities of the FP and EP3 receptors for the two forms of PGA may influence events in vivo.

PGA may act not only on the Mueller muscles [5], but may also influence collagen degradation in the levator muscle complex [9]. Such multiple mechanisms of action, that may also involve interactions between effectors and adipose cells, must be considered when DUES develops. Because the penetration rate or concentration of each drug in the orbital tissue has not been investigated, future studies should be conducted to clarify the mechanism of DUES and differences among PGAs. It is necessary to conduct randomized prospective clinical trials with large numbers of patients to further explore whether relevant ocular/systemic factors are indeed in play and to determine the optimal clinical procedure for evaluation of PGA levels.

TAF displayed a good IOP-lowering effect even in eyes with normal pressure. No IOP elevation (16.6 mmHg over the last three visits before observation, and 16.6 mmHg over the first three visits after observation, $P = 0.84$) or aggravation of the optic disc were seen in the non-instillation eye during the 6 months of observation. In addition, we confirmed that there was no incidence of upper eyelid change on the non-instillation side.

Although we investigated factors associated with DUES, the background of the patients in the DUES-positive and DUES-negative groups should not be compared because of the low rate of incidence. We compared 37 NTG cases (excluding 6 POAG cases) in total. Neither sex ($P = 1.0$), MD ($P = 0.44$), age ($P = 0.11$), refraction ($P = 0.12$), or IOP ($P = 0.45$) reduction affected the incidence of DUES.

One limitation to this study was the small sample size, which would decrease the likelihood of finding a significant relationship with age, sex, MD, refraction, or IOP reduction. However, a search for associations between baseline ocular/systemic factors and DUES occurrence may be useful on the grounds that such analysis may improve the quality of clinical practice. A second limitation is that our follow-up period was rather short, and we did not note DUES

deterioration in our six DUES-positive patients. When the usual duration of glaucoma medication is considered, the follow-up duration should have been longer than 6 months. Third, the assessment procedures for DUES were not standardized as previously. Currently, judgment is made by skilled observers, and is based, to some degree, on subjective measurements. A quantitative noninvasive method based on objective scientific measurements would resolve this issue. Objectivity could be improved by taking pictures from various angles (e.g., front, close up, from an angle, and above) with standard settings for enhanced picture analysis. A numerical index should also be developed to assess the volume change of upper eyelid. Thus, we cannot offer point-by-point discussion of how DUES progresses. Finally, there could be some racial differences in the incidence or prevalence of DUES associated with TAF, BIM, or other PGAs. The results of this report on TAF-induced DUES in Japanese patients do not necessarily apply to non-Asians. Thus, the differences in DUES for each PGA in other races should be investigated in future studies.

In conclusion, BAK-preserved TAF induced DUES in Japanese OAG patients, as has been seen with other PGAs. When prescribing TAF as an initial treatment for IOP control, there remains the possibility of DUES occurrence, even if this may be at a low probability.

Conflicts of interest R. Sakata, None; S. Shirato, None; K. Miyata, None; M. Aihara, None.

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