

Comparison study of intraocular pressure reduction efficacy and safety between latanoprost and tafluprost in Japanese with normal-tension glaucoma

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Purpose: To evaluate and compare the intraocular pressure (IOP) reduction efficacy and safety between the ophthalmic solutions 0.005% latanoprost (Lat) and 0.0015% tafluprost (Taf) in Japanese patients with normal-tension glaucoma (NTG).

Methods: In this randomized nonmasked study, we prospectively enrolled 30 Japanese NTG patients who had used Lat monotherapy for more than 4 weeks, and randomly divided them into the following two groups: 1) Lat-to-Taf group (LT group) and 2) Taf-to-Lat group (TL group). At the beginning of the study, both groups were switched from initial Lat to Lat or Taf for 12 weeks, and then switched over to the other drug (crossover) for 12 additional weeks. At 0, 4, 12, 16, and 24 weeks, we evaluated each patient's IOP, conjunctival injection, and corneal epitheliopathy score, and at 0, 12, and 24 weeks, we evaluated their eyelash changes and pigmentation of the eyelids and irises.

Results: The mean IOP of the LT group (15 eyes) was 10.5, 10.6, and 11.1 mmHg, at 0, 12, and 24 weeks, respectively, whereas that of the TL group (15 eyes) was 11.7, 11.1, and 10.5 mmHg at 0, 12, and 24 weeks, respectively. No significant differences were found between the two groups and in the intragroup comparisons. Moreover, no significant differences were found between Lat and Taf in regard to the conjunctival injection score and corneal epitheliopathy score. Eyelash changes and eyelid and iris pigmentation were similar in both groups.

Conclusion: The findings of this study show that Lat and Taf have equivalent efficacy and safety in Japanese patients with NTG.

Keywords: latanoprost, tafluprost, normal-tension glaucoma, crossover

Introduction

Glaucoma is one of the major leading causes of blindness worldwide.¹ In Japan, glaucoma has become the primary cause of blindness since 2004.² Normal-tension glaucoma (NTG) is the most common type of glaucoma in Japan,³ with a prevalence rate of 3.6% in people over 40 years of age. The ophthalmic solutions 0.005% latanoprost (Lat)^{4,5} and 0.0015% tafluprost (Taf)^{6,7} are topical prostaglandin analogs. Both solutions greatly reduce intraocular pressure (IOP) by increasing the uveoscleral outflow as a prostaglandin F receptor agonist.⁸ Lat was first approved for clinical use in 1996 and has been used globally since then as a first-line drug for the treatment of glaucoma. On the other hand, the IOP reduction efficacy and safety of Taf, first launched in 2008, is reportedly equivalent to that of Lat⁹ for patients with primary open-angle glaucoma or ocular hypertension. Although there have been reports on the efficacy

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of Taf for NTG patients,^{10,11} to the best of our knowledge, no comparison crossover studies have been conducted to investigate the efficacy and safety between Lat and Taf for NTG patients.

In this prospective crossover study involving Japanese NTG patients, the IOP reduction efficacy and safety of Taf were compared with those of Lat.

Subjects and methods

All study procedures were approved by the Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan, and were performed in accordance with the tenets set forth in the Declaration of Helsinki. This study was a randomized nonmasked study. All study participants were recruited between March 2009 and March 2011. We selected and enrolled 30 Japanese NTG patients who had used Lat monotherapy at least 4 weeks at the Glaucoma Special Clinic of Kyoto Prefectural University of Medicine. Written informed consent was obtained from all patients after receiving a detailed explanation of the nature and possible consequences of their participation in the study.

Each of the 30 enrolled patients were randomly divided into one of the following two groups: 1) Lat-to-Taf group (LT group: 15 patients, 7 male eyes and 8 female eyes; mean age: 63.5 ± 11.5 years) and 2) Taf-to-Lat group (TL group: 15 patients, 8 male eyes and 7 female eyes; mean age: 69.1 ± 8.8 years). At the beginning of the study, both groups were switched from initial Lat to Lat or Taf for 12 weeks, and then switched over to the other drug (crossover) to use for 12 additional weeks (Figure 1). At 0, 4, 12, 16, and 24 weeks, we evaluated their IOP, conjunctival injection score (Grades 0–3),¹² and corneal epitheliopathy score (area density [AD] score).¹³ Then, at 0, 12, and 24 weeks, we evaluated adverse events of eyelash changes and pigmentation of the eyelids and irises via a slit-lamp photograph taken at each visit. The incidence of eyelash and pigmentation was judged via slit-lamp photographs, with a comparison

between the current and baseline photographs. In all patients, IOP was measured by using an applanation tonometer (H03 R 90030515; Haag-Streit, Bern, Switzerland) by the same glaucoma specialist throughout the protocol periods, and those IOP measurements were obtained at approximately the same time of day for each patient. If data were available from both eyes, then the right-eye data were used. We evaluated the mean deviation of the Humphrey 30-2 threshold of static visual field program at baseline or within 3 months. Statistical analysis was performed using the Student's *t*-test and Fisher's exact test.

For each patient, Lat and Taf eye drops were prescribed at the Glaucoma Special Clinic. As this was not a masked study, both the patient and the doctor knew which eye drop was being used. A calculated sample size of 15 enrolled subjects per arm providing the power of 80% was based on a noninferiority limit of 1.5 mmHg, a standard deviation of 1.5 mmHg for change in IOP.

Results

There were no dropout cases, and all patients completed the study. Of the total 30 subjects, 28 were newly prescribed Lat, yet 1 subject in both the LT and TL groups used Lat for more than 4 weeks. The backgrounds of the patients are detailed in Table 1. There were no significant differences in age, sex ratio, or mean deviation obtained from Humphrey perimetry sita standard 30-2 between the LT and TL groups.

As for the IOP time course of all subjects, at 0, 12, and 24 weeks, respectively, the mean IOP of the LT group (15 eyes) was 10.5, 10.6, and 11.1 mmHg, whereas that of the TL group (15 eyes) was 11.7, 11.1, and 10.5 mmHg, and no significant differences were found between the two groups (Student's *t*-test) (Figure 2). At 0, 4, and 12 weeks, respectively, the mean IOP of the Lat intragroup (30 eyes) was 10.8, 10.6, and 10.5 mmHg, whereas that of the Taf

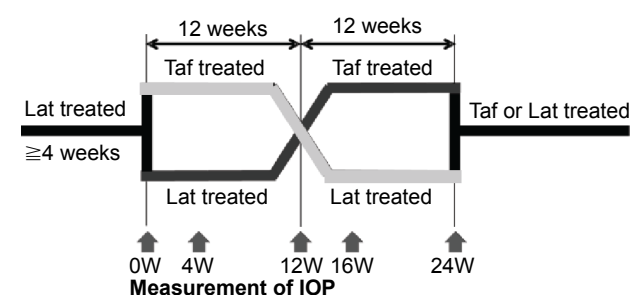


Figure 1 Study design.

Abbreviations: IOP, intraocular pressure; Taf, tafluprost; Lat, latanoprost; W, week.

Table 1 Background of the subjects

	All subjects	LT group	TL group
Number of subjects	30	15	15
Male/female	15/15	7/8	8/7
Mean age (years)	66.3 ± 10.5	69.1 ± 8.8	63.5 ± 11.5
Baseline IOP at study starting (mmHg)	11.1 ± 2.0	10.5 ± 1.7	11.7 ± 2.2
Nonmedication baseline IOP (mmHg)	13.8 ± 2.2	13.9 ± 2.3	13.6 ± 2.0
Baseline MD (dB)	-4.2 ± 4.2	-4.5 ± 5.2	-3.9 ± 3.3
Periods of Lat use before initiation of this study (weeks)	5.5 ± 8.2	6.9 ± 11.4	22.9 ± 73.3

Note: Data presented as mean \pm SD.

Abbreviations: LT, latanoprost to tafluprost; TL, tafluprost to latanoprost; IOP, intraocular pressure; MD, mean deviation; Lat, latanoprost.

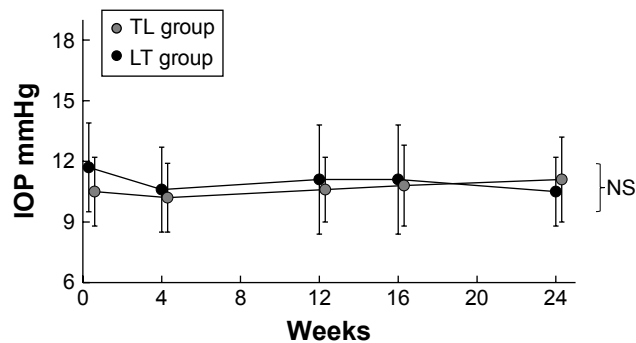


Figure 2 IOP time course of all subjects.

Note: No significant difference in IOP reduction was found between the LT to TL group and the TL to LT group throughout 24 months.

Abbreviations: IOP, intraocular pressure; LT, latanoprost to tafluprost; TL, tafluprost to latanoprost; NS, not significant.

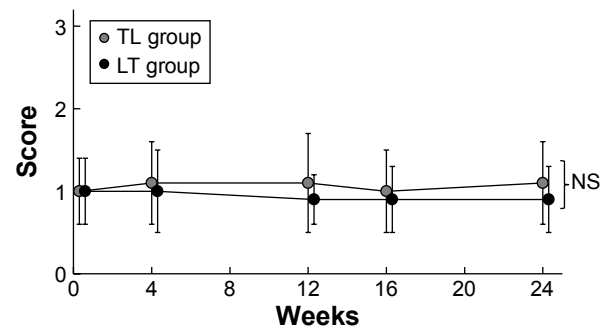


Figure 4 Conjunctival hyperemia score.

Note: No significant difference in conjunctival hyperemia score was found between the two groups.

Abbreviations: LT, latanoprost to tafluprost; TL, tafluprost to latanoprost; NS, not significant.

intragroup (30 eyes) was 10.8, 10.7, and 11.1 mmHg, and no significant differences were found between the two intra-groups (Student's *t*-test) (Figure 3).

The mean conjunctival hyperemia score at 0, 4, 12, 16, and 24 weeks, respectively, was 1.0 ± 0.4 , 1.0 ± 0.5 , 0.9 ± 0.3 , 0.9 ± 0.4 , and 0.9 ± 0.4 in the LT group and 1.0 ± 0.4 , 1.1 ± 0.5 , 1.1 ± 0.6 , 1.0 ± 0.5 , and 1.1 ± 0.5 in the TL group, and no significant differences were found between two groups (Student's *t*-test) (Figure 4). The respective mean AD score at 0, 4, 12, 16, and 24 weeks was 0.5 ± 0.9 , 1.0 ± 1.4 , 0.7 ± 1.0 , 0.9 ± 1.4 , and 0.7 ± 1.0 in the LT group and 1.0 ± 1.3 , 0.7 ± 1.0 , 0.7 ± 1.0 , 0.5 ± 1.0 , and 0.8 ± 1.3 in the TL group, and no significant differences were found between the two groups (Student's *t*-test) (Figure 5).

The rates of the adverse events of eyelash change and eyelid and iris pigmentation induced by Lat or Taf are shown in Table 2. The incidence of eyes showing increased eyelash length was 30.0% by Lat and 26.7% by Taf, and the incidence of eyes showing increased eyelash amount was 16.7% by Lat and 30.0% by Taf. The incidence of eyes showing increased eyelid pigmentation was 3.3% by Lat and 20.0% by Taf, and

the incidence of eyes showing increased iris pigmentation was 6.7% by Lat and 3.3% by Taf. There was no significant difference in the incidence of eyelash change (length and amount) as well as eyelid and iris pigmentation between the two groups (Fisher's exact test).

Discussion

Although there have been reports on the efficacy of Taf for NTG patients, to the best of our knowledge, this present study is the first crossover prospective report to investigate and compare IOP reduction efficacy and safety between Lat and Taf in NTG patients. In this study, no significant differences were found between Lat and Taf in regard to IOP reduction effects, conjunctival hyperemia score, and corneal epitheliopathy score, as well as eyelash change and eyelid and iris pigmentation. It has been reported that conjunctival hyperemia becomes stronger when switching from Lat to travoprost or bimatoprost,^{14,15} and the same tendency was found to be true in this present study when switching from Lat to Taf. Although there were no statistically significant differences, elongation of eyelash length was more frequently found in

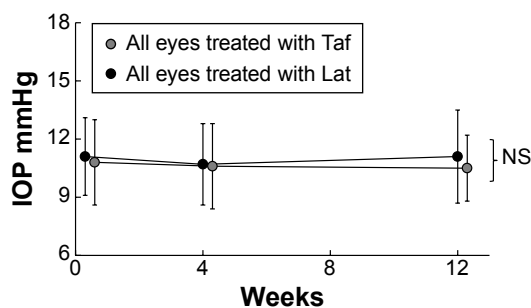


Figure 3 IOP reduction time-course between all subjects of the Lat and Taf group.

Note: No significant difference in IOP reduction was found between the two groups.

Abbreviations: IOP, intraocular pressure; Lat, latanoprost; Taf, tafluprost; NS, not significant.

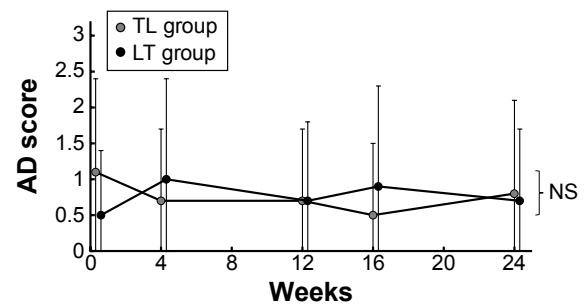


Figure 5 Corneal epitheliopathy score (AD score).

Note: No significant difference in AD score was found between the two groups.

Abbreviations: AD, area density; LT, latanoprost to tafluprost; TL, tafluprost to latanoprost; NS, not significant.

Table 2 Incidence of eyes showing increased eyelash and incidence of eyes showing increased pigmentation at 3 months by latanoprost and tafluprost

	Incidence of eyes showing increase of eyelash				Incidence of eyes showing increase of pigmentation			
	Length		Amount		Eyelid		Iris	
	n	%	n	%	n	%	n	%
Effect by Lat	9	30.0	5	16.7	1	3.3	2	6.7
Effect by Taf	8	26.7	9	30.0	6	20.0	1	3.3
No effect by both Lat and Taf	13	43.3	16	53.3	23	76.7	27	90.0

Abbreviations: Lat, latanoprost; Taf, tafluprost.

Lat, whereas increased eyelash amount was more frequently found in Taf. Since the patients involved in this study were already users of Lat for over 1 month, it was difficult to make a simple comparison between the two drugs in regard to the adverse events of newly appearing eyelid and iris pigmentation or eyelash elongation. In this study, there was a tendency of more eyelid pigmentation with Taf than with Lat. According to past reports for eyelash length, eyelash amount, eyelid pigmentation, and iris pigmentation, the appearance rate was 0–25.8/0.38%, 26/46%, 1.5–6.0/1.08%–4%, and 0–12.3/4.0% with Lat/Taf,^{7,13,14,16–21} respectively. Our results were nearly the same as those of the previous reports, except for iris and eyelid pigmentation. Our findings showed that eyelid pigmentation was greater with Taf than with Lat, yet with no significant difference. We must investigate further eyelid pigmentation induced by Taf.

It should be noted that this study did include some limitations. The first limitation was that this was not a masked study, as both the subjects and the attending doctor knew which eye drop was being used. The second limitation was that since the baseline IOP of all subjects using Lat was low, it was difficult to find the switching efficacy of the eye drop.

Conclusion

The findings of this study show that Lat and Taf have equivalent safety and efficacy in Japanese NTG patients with low IOP.

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actual paper, however, has never been published. Clinical trial number Umin-CTR, UMIN000002017.

Disclosure

The authors report no conflicts of interest in this work.

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