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CLINICAL INVESTIGATION

Efficacy and safety of switching to travoprost/timolol fixed-combination therapy from latanoprost monotherapy

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Abstract
Purpose To prospectively assess the efficacy of switching to a travoprost/timolol fixed-combination (TTFC) therapy from latanoprost monotherapy.
Methods This was a prospective, open-label study in which patients with either primary open-angle glaucoma or ocular hypertension who had been undergoing latanoprost monotherapy for at least 3 months were enrolled. Baseline was defined as the time when the subjects were started on latanoprost monotherapy. Examination periods were defined as 1, 2, and 3 months the switch to TTFC therapy, and 1–2 months after the switch back to latanoprost monotherapy. The parameters examined were intraocular pressure (IOP), conjunctival hyperemia, and corneal erosion, as well as blood pressure and heart rate. A survey was conducted 1 and 3 months after the switch to TTFC therapy with a focus on each subject's impressions.
Results Among the 70 enrolled subjects, the 58 (29 men, 29 women) who completed the protocol were analyzed. The IOP before and at 1, 2, and 3 months after the switch to TTFC therapy was measured and again after the switch back to latanoprost monotherapy. The results indicated that TTFC therapy significantly reduced the IOP ($P < 0.001$) and significantly decreased the heart rate, but it did not significantly change either the systolic or diastolic blood pressure. TTFC therapy also did not significantly change either the conjunctival hyperemia or corneal erosion. In the questionnaire, the patients indicated that their impression was that there was no significant difference between the two ophthalmic solutions.
Conclusions Compared to latanoprost monotherapy, TTFC therapy significantly reduced IOP and decreased the heart rate in the patient cohort. No differences were found in terms of patients' impressions.

Keywords Glaucoma · Travoprost/timolol fixed combination · Latanoprost · Intraocular pressure

Introduction

Anti-glaucoma ophthalmic solutions are the primary treatment for glaucoma. However, as patients with glaucoma have relatively mild subjective symptoms until their condition worsens and the efficacy of ophthalmic solutions is not easily noticeable, both the adherence to and continuity of treatment are reportedly poor [1, 2]. The number of glaucoma patients who use two or more anti-glaucoma ophthalmic solutions concurrently is increasing in both Japan [3] and other countries [4]. It has been reported that the use of fewer ophthalmic solutions would decrease the burden on patients and improve adherence to treatment while at the same time reducing adverse effects [5, 6].

Fixed-combination ophthalmic solutions have been gaining approval for clinical use. Three solutions are currently available in Japan. One of these, the travoprost/timolol fixed-combination (TTFC), which contains both travoprost and timolol, has been found to significantly reduce intraocular pressure (IOP) in patients receiving monotherapy [7, 8] and to achieve comparable IOP reducing effects as latanoprost and timolol solutions given

For the A-LaTT Study Group.

The members of the A-LaTT Study Group are listed in Appendix.

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separately [9, 10]. Improved adherence has also been reported as compared to the use of either travoprost or timolol separately [11–13]. However, as little time has passed since the TTFC and other fixed-combination therapies have been approved for glaucoma, there is as yet little information available on the use of such combination therapies in Asian glaucoma patients, including Japanese patients, compared to the many reports that focus on Caucasian populations [14].

The objective of this study was to examine the effects of switching Japanese glaucoma patients being treated with latanoprost to TTFC therapy on IOP reduction and other parameters, including the occurrence of local and systemic side effects.

Methods

This study was performed as a prospective, open-label, multicenter trial, approved by the Ethics Committee of the University of Yamanashi and conducted in accordance with the Helsinki Declaration. All participants gave written informed consent.

Patients

The subjects were patients with primary open-angle glaucoma, including normal-tension glaucoma, or with ocular hypertension, who had been receiving continuous latanoprost monotherapy for at least 3 months and for whom further IOP reduction was judged necessary by the attending physician. The following patients with the following conditions/medical histories were excluded from the study: chronic or recurrent uveitis, ocular injury within 6 months prior to the study, history of intraocular surgery, including laser treatment within 2 years before this study; conditions preventing IOP measurement by applanation tonometry; arrhythmia, asthma, and other contraindications to beta blockers. In addition; physicians excluded any patient whose participation was regarded as inappropriate.

Study protocol

Mean IOP measured at the time of study entry and prior to the switch to TTFC therapy was defined as the baseline IOP. Examinations were performed at 1, 2, and 3 months after the switch to TTFC without a washout period. TTFC was instilled once every morning. The patients switched back to latanoprost monotherapy without a washout period after 3 months of continuous TTFC treatment and underwent re-examination 1–2 months thereafter. The duration of the treatment period on latanoprost monotherapy after the switch back from TTFC therapy was kept the same as that prior to the initial switch to TTFC therapy. The study design and parameters examined are shown in Table 1. IOP measurements were performed by Goldman applanation tonometry, and the measurements were repeated twice and then averaged. The measurement time for each patient was decided upon based on the time of baseline measurement, so the measurements were performed within 2 h either before or after this time. Corneal erosion was evaluated based on the method described in a previous study [15]. In brief, two parameters of corneal erosion, area and density, were graded on a scale from A0 through to A3 and from D0

Table 1 Study protocol and parameters examined

	entry	baseline	1M	2M	3M	Switch back
Background	√	√				
IOP (GAT)	√	√	√	√	√	√
Corneal erosion	√	√	√	√	√	√
Conjunctival hyperemia		√	√	√	√	√
BP, PR		√	√	√	√	√
BCVA		√			√	
Adverse effect			√	√	√	√
Questionnaire			√		√	
latanoprost	⟷	⟷			⟷	⟷
TTFC		⟷	⟷	⟷	⟷	

IOP intraocular pressure, *GAT* Goldmann applanation tonometry, *BP* blood pressure, *PR* pulse rate, *BCVA* best-corrected visual acuity, *TTFC* travoprost/timolol fixed-combination

Table 2 Items in the questionnaire and their grades

Items of questionnaire	Grade		
Itching	None	Mild	Severe
Foreign body sensation	None	Mild	Severe
Blurred vision	None	Mild	Severe
Hyperemia	None	Mild	Severe
Dry eye sensation	None	Mild	Severe
Which ophthalmic solutions preferred	TTFC	Latanoprost	No preference

through to D3. Bulbar conjunctival hyperemia was classified into four stages from grade 0 through to grade 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Sample photo images were employed to classify corneal erosion and bulbar conjunctival hyperemia. Blood pressure and heart rate measurements were performed with the patient in the sitting position at baseline and at 1, 2, and 3 months after the switch to TTFC therapy and after the switch back from TTFC. A questionnaire survey (Table 2) on the use and overall comfort of the ophthalmic solutions was conducted at 1 and 3 months after the switch to TTFC.

Statistical analysis

Data were analyzed using the JMP 8.0 software program (SAS Institute, Cary, NC) and the results presented as the mean ± standard deviation (SD). Differences in results were assessed using repeated measures analysis of variance (ANOVA) and contingency table analysis. Correlation between two parameters was investigated using Pearson's correlation coefficient. P values of <0.05 were considered to be significant.

Results

Enrolled patients

A total of 70 patients (35 men, 35 women; age 24–85 years; mean age 66.5 ± 14.1 years) were enrolled in this study. At the time of entry, the mean latanoprost administration period was 44.8 months (range 3–135 months, median 36 months). In all, 58 patients completed the study (age 24–85 years, mean age 65.6 ± 14.4 years). The mean duration of the latanoprost administration period was 45.0 months (range 3–135 months, median 39 months). Intraocular surgery had been performed on seven eyes without notable complications, and in all cases, 2 years or more had elapsed since the surgery. None of the patients had a history of ocular injury. Among those patients who completed the study protocol, 42 patients measured their IOP in the morning and 16 in the afternoon.

Causes of dropout

Of the 12 cases of dropout, five were possibly due to the TTFC and included one case each of ocular itching, blepharitis, and foreign body sensation, and two cases of dyspnea. In all cases, the symptoms were mild and improved after the discontinuation of the TTFC. It is unclear whether patients with dyspnea showed irregular rhythm because they quit using the eyedrops before their revisit to the hospital. Three patients discontinued the study for reasons that were judged to be unrelated or only mildly related to the TTFC. One case of elevated IOP and one case of uveitis were observed after the switch to TTFC; however, these conditions did not reappear upon the re-administration of TTFC. One patient had cerebral infarction during the course of the study, although its association with TTFC was minor as the patient had a history of cerebral infarction. Two patients violated the protocol and another two patients requested discontinuation, although no side effects were observed. The total dropout ratio was 17.1 %.

Changes in IOP

Baseline IOP was 16.8 ± 2.7 mmHg; in comparison, at 1, 2, and 3 months after the switch to TTFC, the IOP was 14.6 ± 3.2, 14.3 ± 3.1, and 14.5 ± 2.8 mmHg, respectively, which is a significant decrease relative to the baseline value ($P < 0.001$, repeated measures ANOVA) (Fig. 1). After the switch back to latanoprost monotherapy, the IOP was 16.2 ± 3.4 mmHg, which is significantly higher than that measured during TTFC treatment ($P < 0.001$, repeated measures ANOVA). The IOP after the switch back to latanoprost was not significantly different from the baseline IOP. The rates of IOP reduction are shown in Fig. 2. The mean IOP reduction rate during the 3-month period following the switching to TTFC

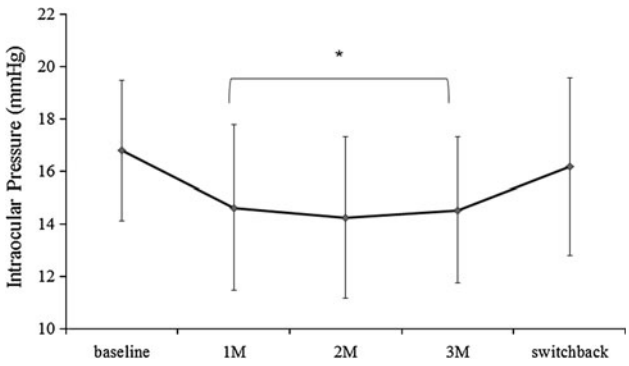

Fig. 1 Time-course of intraocular pressure (IOP). *$P < 0.001$ versus baseline and the switch back to latanoprost monotherapy [repeated measures analysis of variance (ANOVA)]. *M* Month. *Bar* SD

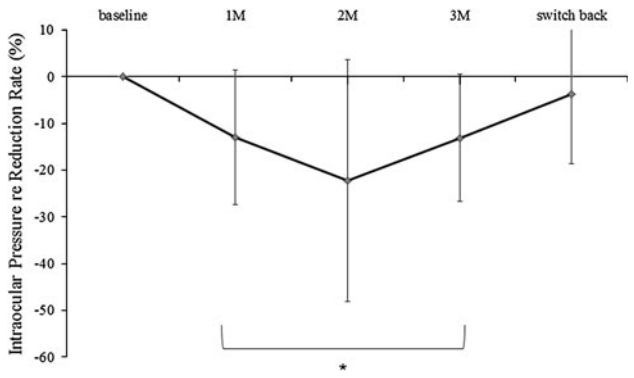

Fig. 2 Time-course of IOP reduction rate. *$P < 0.001$ versus switch back to latanoprost monotherapy (repeated measures ANOVA). *Bar* SD

therapy was −13.5 ± 11.8 %. After the switch, the rates of IOP reduction at 1, 2, and 3 months were not significantly different. As shown in Fig. 3, a significant positive correlation was found between the baseline IOP and the amount of IOP reduction, while the relationship between the IOP reduction rate and baseline IOP were not significantly correlated.

Topical adverse effects

A trend toward a slightly increased congestion of the palpebral conjunctiva was observed after the switch to TTFC; however, there were no significant differences (Fig. 4). In terms of corneal erosion, neither area nor density differed significantly between before and after the switch to TTFC therapy (Fig. 5a, b). There were no significant differences in best-corrected visual acuity between baseline and 3 months after the switch to the TTFC.

Changes in blood pressure and heart rate

There were no significant changes in either systolic or diastolic blood pressure during the time-course of the study (Fig. 6a). In contrast, heart rate decreased significantly after the switch to TTFC therapy, returning to the baseline level after the switch back to latanoprost (Fig. 6b). The mean heart rate decrease during the 3-month period after the switch to TTFC was −9.1 ± 9.8 %.

Patient questionnaires

In the questionnaire survey conducted 1 month after the switch to TTFC monotherapy, more than half the patients indicated that the subjective symptoms associated with TTFC therapy were similar to those experienced during latanoprost monotherapy for all of the items listed in the questionnaire (Fig. 7a). For all items, more patients

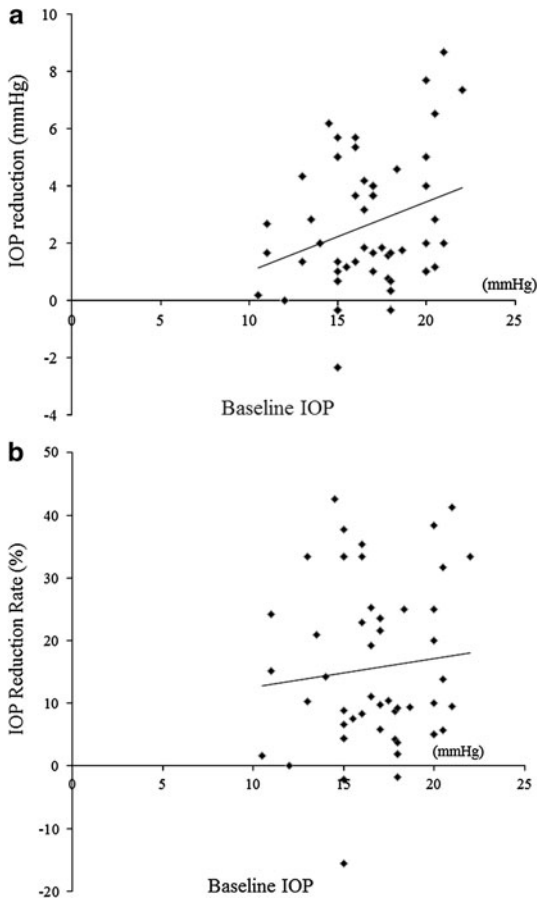

Fig. 3 Relationship between baseline IOP and IOP reduction. **a** Relationship between baseline IOP and amount of IOP reduction ($R^2 = 0.0832$, $P = 0.03$), **b** relationship between baseline IOP and IOP reduction rate ($R^2 = 0.009$, $P = 0.48$)

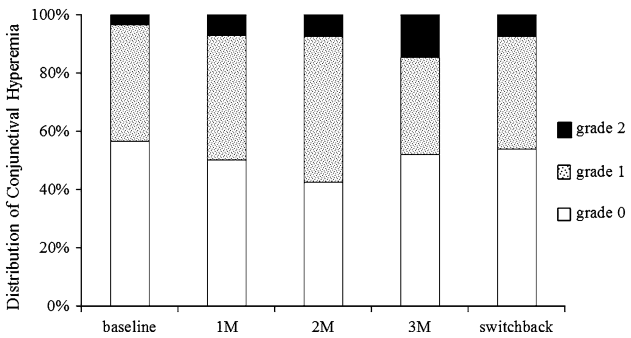

Fig. 4 Time-course of conjunctival hyperemia

reported improved symptoms than worsened symptoms. None of the patients reported worsening of dryness of the eye. In the questionnaire survey conducted 3 months after the switch to TTFC therapy, 80 % or more of the patients indicated no problematic subjective symptoms in any of the items (Fig. 7b). Compared to 1 month after the switch to TTFC therapy, one patient (0.54 %) complained of itching, and two patients (1.1 %) complained of hyperemia; no

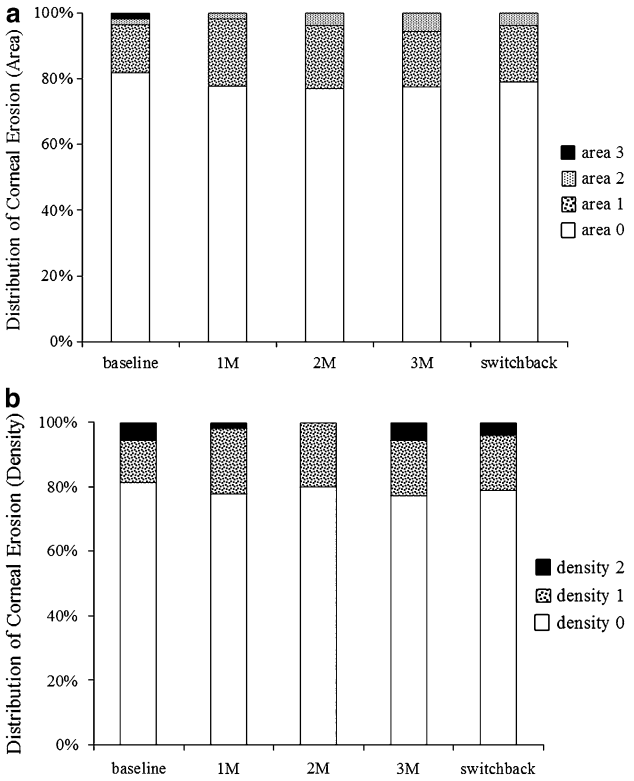

Fig. 5 Time-course of corneal erosion in terms of area (**a**) and density (**b**)

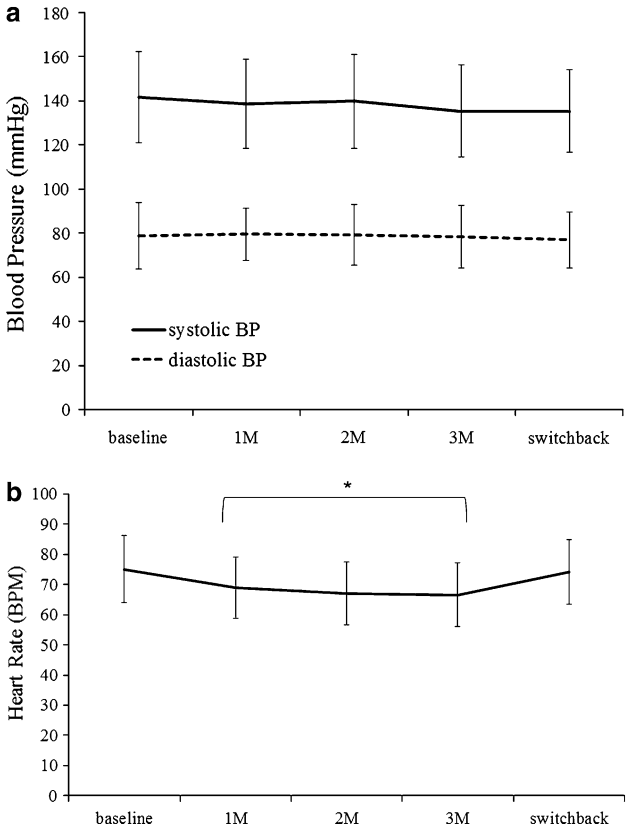

Fig. 6 Time-course of systemic circulatory parameters. **a** Blood pressure, **b** pulse rate. *BP* Blood pressure, *BPM* beat per minute. $*P < 0.001$ for baseline versus the switch back to latanoprost monotherapy (repeated measures ANOVA). *Bar* SD

exacerbation was noted in the other items. Three months after the switch to TTFC, when patients were asked if they preferred latanoprost or TTFC, 68 % responded that they had no preference, 27 % preferred TTFC, and 5 % chose latanoprost.

Discussion

The clinical use of combination ophthalmic solutions was not initiated in Japan until 2010 and, consequently, only a few evidence-based reports on the efficacy and safety of combination ophthalmic solutions in Japanese patients have been published. The aim of our prospective, open-label, multicenter study was to assess the switch-back effect of using such combination ophthalmic solutions and thus supplement current knowledge of their efficacy and safety. In this study, patients were switched from TTFC therapy back to latanoprost monotherapy after 3 months of treatment. Therefore, we believe that the results of this study are solid.

TTFC therapy led to significant IOP reduction compared to latanoprost monotherapy, with a mean decrease of 2.4 mmHg (13.5 %) during the 3-month period following the switch to the TTFC. Pfeiffer et al. [7] report that switching to TTFC therapy from latanoprost monotherapy led to a decrease in IOP of 6.3 mmHg, which is a larger decrease than that found in our study. One possible explanation for this difference may be that the IOP of patients in Pfeiffer et al.'s study was higher prior to the switch to the TTFC. Barnebey et al. [16] report IOP reductions ranging from 0.9 to 2.4 mmHg after the switch from travoprost to the TTFC, which are closer to the results of our study.

Conjunctival hyperemia is frequently reported in patients following topical ocular administration of travoprost [7, 16–19]. In our study, we observed a slight increase in the occurrence of conjunctival hyperemia, but the change was not statistically significant. In addition, in their answers to the questionnaires, only a few patients complained that their hyperemia had worsened with the duration of latanoprost monotherapy, suggesting that there are no issues associated with its clinical use. Although the reason is still unknown, with prostaglandin analogues, long-term use can lead to an improvement of local symptoms. As the subjects of this study had been using latanoprost for at least 3 months (median 39 months), hyperemia due to the switch to TTFC therapy may not have been significant.

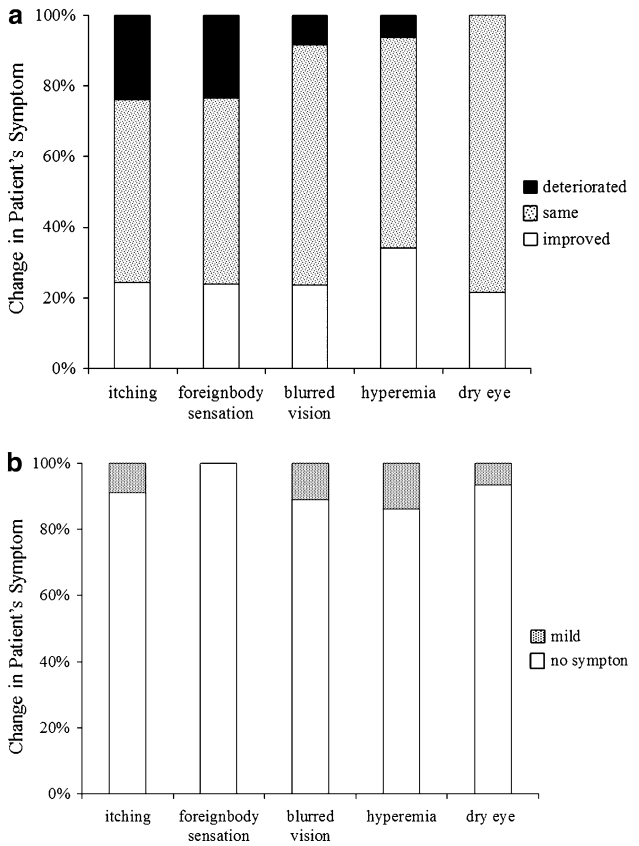

Fig. 7 Results of the patient questionnaire at 1 month (**a**) and 3 months (**b**) after the switch to TTFC therapy

Polidronium chloride is used as a preservative in the TTFC instead of the preservative commonly used in many ophthalmic solutions, benzalkonium chloride (BAC). It has been reported that polidronium chloride does not affect the ocular surface as much as BAC [20, 21] and, therefore, the expectation has been that the former would be useful in solutions used to treat corneal disorders. However, the findings of our study did not reveal any significant differences between latanoprost monotherapy and TTFC therapy in terms of corneal disorders. Kitazawa et al. [22] found no differences between BAC-containing TTFC and non-BAC-containing TTFC in terms of corneal disorders, which is consistent with the results of our study. However, it is possible that the lack of differences found in our study was due to the fact that our patients presented with either none or only mild corneal disorders before being switched to TTFC therapy. Many of the patients with glaucoma use the same or more than two kinds of anti-glaucoma ophthalmic solutions [3], and Cho et al. [23] reported that a fixed-combination anti-glaucoma ophthalmic solution is beneficial in reducing adverse ocular surface changes in long-term use. Consequently, TTFC may be a better choice for glaucoma treatment over the long term.

During the 3-month period following the switch to TTFC, there was a significant decrease in heart rate (9.1 %) but no change in blood pressure. As TTFC contains timolol, a beta blocker, its impact on circulatory function is predictable and expected, i.e., the presence of timolol explains the lack of effect on blood pressure and significant decrease in heart rate. Previous reports suggest that timolol decreases the heart rate and also depresses respiratory function [24–26]. Two patients in our study cohort complained of dyspnea. It has been reported that the long-term use of beta blockers can lead to a subclinical increase in bronchial reactivity, even in healthy individuals [27], and reversible breathing disorders in the elderly [28]. As all combination ophthalmic solutions currently available in Japan contain timolol, it is necessary to carefully monitor circulatory function and respiratory function when combination ophthalmic solutions are prescribed in the future.

This study had a relatively high dropout rate of 17.1 %, including five cases (7.1 %) involving side effects from TTFC use. This figure is quite a bit higher than those previously reported [7, 16], and although no reason for this difference could be found, ethnic differences may contribute to the prevalence of side effects. None of the side effects observed in our patients was serious, but careful attention should be paid to the occurrence of side effects in patients on TTFC therapy.

There was a subtle trend toward improvement in overall comfort after the switch to TTFC therapy, and symptoms tended to resolve after TTFC therapy had been continued for 3 months. Although a timolol-containing ophthalmic solution usually aggravates the dry eye sensation among patients with glaucoma when used as monotherapy, TTFC therapy was able to alleviate the timolol-induced dry eye sensation due to the presence of polidronium chloride, which does not affect the ocular surface as much as BAC. When deciding between the two treatment options, the ultimate preference for TTFC was slightly stronger.

In this study, IOP measurement was performed only during outpatient visits and we did not investigate the efficacy of TTFC therapy for IOP reduction at night. The efficacy of beta blockers in IOP reduction is poor at night [29], necessitating further research in this area.

In conclusion, the efficacy of TTFC, a travoprost/timolol fixed-combination ophthalmic solution, in IOP reduction was compared with that of latanoprost monotherapy. In our Japanese patient cohort, TTFC significantly reduced IOP compared to latanoprost monotherapy. Furthermore, patients were positively impressed with its use. Glaucoma treatment that optimizes the advantages of combination ophthalmic solutions, such as improved adherence and reduction of side effects, is required.

Appendix: Members of the A-LaTT Study Group

This study was performed by A-LaTT study group. Members of this group in addition to the first author are: Hiroshi Takahashi (University of Yamanashi, Yamanashi), Fumihiko Mabuchi (University of Yamanashi, Yamanashi), Tatsuya Chiba (University of Yamanashi, Yamanashi), Toshie Furuya (University of Yamanashi, Yamanashi), Hiroyuki Iijima (University of Yamanashi, Yamanashi), Satoshi Kogure (Kogure Eye Clinic, Yamanashi), Osamu Hosaka (Hosaka Eye Clinic, Yamanashi), Tetsunori Saito (Saito Eye Clinic, Yamanashi), Takaharu Tokunaga (Meru Eye Clinic, Tokyo), Fumiko Kashiwagi (Kashiwagi Eye Clinic, Yamanashi), Jhoji Tanabe (Tanabe Eye Clinic, Yamanashi), Satoshi Yamaguchi (Yamaguchi Eye Clinic, Yamanashi), Takashi Shibuya (Shibuya Eye Clinic, Yamanashi), Tadayuki Tsuchiya (Tsuchiya Eye Clinic, Yamanashi), Toyoaki Tsumura (Fussa Hospital, Tokyo), Hiroki Akiyama (Akiyama Eye Clinic, Shizuoka), Kiyotaka Ishijima (Irumagawa Hospital, Saitama), and Shigeo Tsukahara (Tsukahara Eye Clinic, Yamanashi).

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