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Switching Study of Tafluprost/Timolol Fixed-Combination Ophthalmic Solution, Following Unfixed Combination of Tafluprost Ophthalmic Solution 0.0015% and Timolol Ophthalmic Gel-Forming Solution 0.5%

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Abstract

Purpose: Fixed-combination medication to treat glaucoma can reduce intraocular pressure (IOP) without negative effects of concomitant medication. Tafluprost/timolol fixed-combination ophthalmic solution (TTFC) has been reported to show similar effectiveness in lowering IOP, compared with concomitant use of its component drugs, tafluprost and timolol. However, the difference in IOP-lowering effects between TTFC and concomitant use of tafluprost and gel-forming timolol is unknown. Hence, we conducted this switching study from tafluprost and gel-forming timolol to TTFC in glaucoma patients undergoing multi-drug therapy. **Design:** Multi-center, open-label, interventional clinical study. **Methods:** Twenty-eight patients (28 eyes; safety analysis set) with primary open-angle glaucoma and ocular hypertension, who had completed the 4-week-concomitant phase of tafluprost and gel-forming timolol, were treated for 8 weeks with TTFC. IOP, adherence, ocular surface safety, and the usability of ophthalmic solution were compared before and after switching. This study was approved by the ethics committees of Kitasato University Hospital and all other study sites. All patients provided written informed consent to participate. **Results:** IOP at 8 weeks after switching

was significantly lower than before switching (P = 0.0001) in the efficacy analysis set (n = 24). The self-reported adherence rate remained high after switching; moreover, there was no meaningful change in ocular surface safety. Patient questionnaires regarding usability of medication revealed that 85.7% of patients preferred their instillation prescription after switching, including TTFC. Among the safety analysis set (n = 28), no adverse events were reported in relation to the study drug. **Conclusion:** TTFC showed greater IOP reduction than concomitant therapy. Thus, TTFC may be a better option in glaucoma patients than concomitant therapy.

Keywords

Glaucoma, Intraocular Pressure, Switching, Tafluprost/Timolol Fixed-Combination, Timolol Gel-Forming Solution

1. Introduction

Glaucoma is a chronic disease that is characterized by irreversible progression of optic neuropathy and visual field defects, [1] and is the leading cause of irreversible blindness worldwide [2]. The onset and progression of glaucoma can be suppressed by lowering intraocular pressure (IOP) [3] [4] [5]. Accordingly, IOP-lowering therapy is critical in the treatment of glaucoma.

Various worldwide clinical practice guidelines for glaucoma recommend that treatment begins with monotherapy [6] [7] [8]. However, the monotherapy approach often cannot achieve target IOP; consequently, multiple medications are used concomitantly. However, concomitant multiple medication therapy might decrease adherence. Moreover, multiple medication therapy may cause problems related to the interactions among drugs, such as the washout effect, which reduces the efficacy of instillation [9] [10] [11]. In addition, the onset of adverse reactions associated with increased exposure to preservatives is a notable concern [12] [13].

To alleviate these issues, fixed-combination ophthalmic solutions can be used. The use of such fixed-combination drugs allows the inclusion of additionally active pharmaceutical ingredients without increasing the number of medication bottles; thus, issues with concomitant therapies (e.g., decreased adherence, washout effects, and increases in preservative exposure) can be avoided.

Tafluprost/timolol fixed-combination ophthalmic solution (TTFC) has been reported to be non-inferior to concomitant use of its component drugs (*i.e.*, once-daily tafluprost ophthalmic solution 0.0015% and twice-daily timolol ophthalmic solution 0.5%) in lowering IOP [14]. However, the differences in IOP-lowering effects of TTFC and concomitant administration of its component drugs, including the use of once-daily timolol ophthalmic gel-forming solution 0.5% (commonly used in clinical practice), are not yet known. Studies with multiple medications that are often used in clinical practice, including TTFC, have

also not been conducted.

The present study was conducted in six hospital-based sites to compare IOP-lowering effects in glaucoma patients on multi-drug treatment, before and after switching from concomitant use of tafluprost and gel-forming timolol to TTFC. Adherence, ocular surface safety, and the usability of ophthalmic solution were also compared.

2. Materials and Methods

2.1. Study Design

The present study was conducted as a multi-center, single-arm, open-label, interventional clinical study. The study was conducted in accordance with the Declaration of Helsinki and the 2014 Ethical Guidelines for Medical and Health Research Involving Human Subjects (published by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare) after obtaining approval from the ethics committees of the core facility (Kitasato University Hospital) and all five other study sites. All patients provided written informed consent to participate in the study. This study is registered under the UMIN Clinical Trials Registry (Registration No. UMIN000016885, 23/03/2015).

2.2. Patients and Study Eye Selection

The study population comprised patients of either sex who were ≥20 years of age; were diagnosed with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), or ocular hypertension (OH); met all of the following inclusion criteria for at least one eye; and did not meet any of the following exclusion criteria. Inclusion criteria: 1) concomitant use of three drugs, *i.e.*, a preserved tafluprost ophthalmic solution 0.0015% (TAPROS® ophthalmic solution 0.0015%, Santen Pharmaceutical Co., Ltd., Osaka, Japan), a timolol ophthalmic gel-forming solution 0.5% (TIMOPTOL® XE ophthalmic solution 0.5%, Santen Pharmaceutical Co., Ltd.), and another glaucoma ophthalmic solution (either a carbonic anhydrase inhibitor, an α_1 blocker, or an α_2 agonist); 2) a mean deviation value exceeding −24 dB (as determined by static perimetry within 2 months before study initiation), or Kozaki's classification of up to stage IV (as determined by dynamic perimetry); and 3) a corrected visual acuity of not lower than 0.7. Main exclusion criteria: 1) patients with severe cataracts or other conditions that may interfere with funduscopy and other examinations; 2) patients with active extraocular disease, eye or eyelid inflammation, or infection; 3) patients with any corneal abnormalities or other diseases that may interfere with accurate IOP measurements using an applanation tonometer; 4) patients with a history of keratorefractive surgery; 5) patients who underwent intraocular surgery (e.g., laser trabeculoplasty, cataract surgery, or glaucoma surgery) within 6 months before study initiation; 6) patients anticipated to require eye disease surgery within the study period; and 7) patients undergoing treatment with any

adrenocorticosteroids (topical application to the skin, outside of periocular regions is permitted). If both eyes were eligible, the eye with higher IOP at Week 0 was chosen as the test eye; if the IOP was similar in both eyes, the right eye was chosen. The calculated sample size for this study was 32 patients, based on the following assumptions with reference to a previous study; [14] the change in IOP was 0 mmHg after switching, the non-inferiority margin was established as 1.5 mmHg, standard deviation was 2.5 mmHg, and power was 90% (paired *t*-test with a 5% level of significance). Thus, the target sample size was 40 patients, to allow for possible dropouts.

2.3. Study Procedure

An outline of the present study is shown in Figure 1. During the concomitant phase, beginning from the day informed consent was obtained (Week −4) until the day before Week 0 began, gel-forming timolol was instilled once daily in the morning and tafluprost was instilled once daily in the evening. During the fixed-combination phase (Week 0 to Week 8), TTFC (preserved TAPCOM® combination ophthalmic solution, Santen Pharmaceutical Co., Ltd.) was instilled once daily in the evening. For all other concomitant glaucoma ophthalmic solutions, changes and discontinuation of drug administration and changes in dosage and administration were prohibited, beginning prior to study initiation and continuing throughout the study period.

2.4. Data Collection

The test parameters evaluated in the present study included: visual acuity and visual field (static or dynamic) measured at Week −4 and Week 8. If a patient underwent a visual field test within 2 months prior to study initiation, the

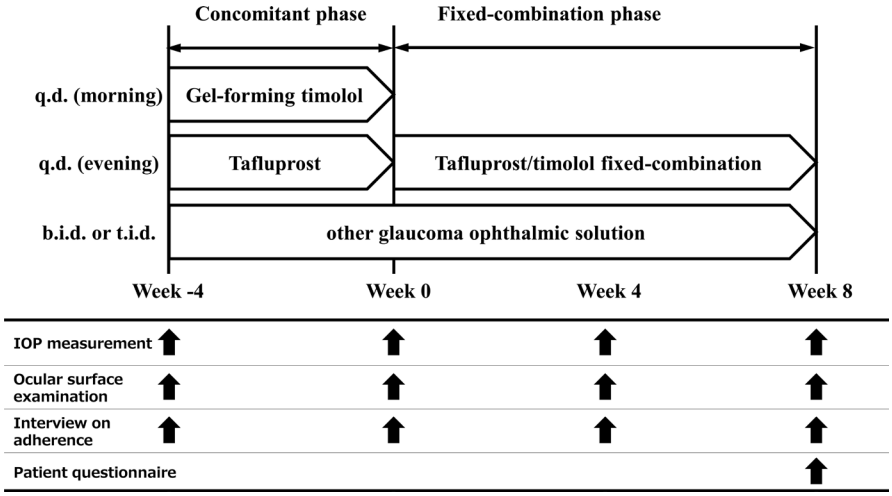

Figure 1. Study outline. During the concomitant phase, gel-forming timolol and tafluprost were instilled in the morning and evening, respectively. During the fixed-combination phase, tafluprost/timolol fixed-combination was instilled in the evening. Other glaucoma ophthalmic solutions were instilled throughout the study period without any changes. Abbreviation: IOP, intraocular pressure.

resulting data were permitted for use in the study. Adherence rate and IOP were measured at all visits. The status of adherence was evaluated via patient self-reporting, using a four-grade rating system: 1) 100%; 2) ≥80% and <100%; 3) ≥60% and <80%; and 4) <60%. IOP was measured at 11:00 a.m. (±1 h) if possible. Two IOP measurements were performed using Goldmann applanation tonometry. If the difference between the two measurements was not <2 mmHg, a third measurement was performed. Ocular surface findings were obtained using a slit-lamp microscope at all visits. Corneal epithelial disorders were evaluated using the area density classification score (AD score), in which classification was performed according to area (three grades) and density (three grades) with fluorescein staining. [15] Ocular hyperemia was evaluated using a five-grade rating system: 0, no hyperemia; 1+, localized very mild hyperemia; 2+, mild hyperemia in the palpebral conjunctiva or bulbar conjunctiva; 3+, moderate hyperemia in the palpebral conjunctiva or bulbar conjunctiva; and 4+, severe hyperemia in the palpebral conjunctiva or (and) bulbar conjunctiva. Funduscopy was conducted at all visits, and adverse events were recorded during the study period. A patient questionnaire was administered at Week 8, with questions regarding changes (positive change, no change, or negative change) in five aspects (frequency of forgetting to instill, usability of container, instillation comfort, blurred vision, and ocular hyperemia) after switching, as well as desired combinations of ophthalmic solutions.

2.5. Data Analysis

The primary endpoint was IOP changes between Week 0 and Week 8 using paired *t*-tests. IOP changes between Week 0 and Week 4 were evaluated in a similar manner. The mean values of two IOP measurements were used for the evaluation at each visit. If a third measurement was performed, the median for the three measurements was used for the evaluation. Changes in AD score between Week 0 and Week 4 or Week 8 were evaluated using total area + density scores assessed in three grades: Improved (improvement by a score of ≥1), Unchanged, and Worsened (aggravation by a score of ≥1). Hyperemia score changes between Week 0 and Week 4 or Week 8 were also evaluated in three grades: Improved (improvement by a score of ≥1), Unchanged, and Worsened (aggravation by a score of ≥1). The responses to the patient questionnaire were standardized based on three grades: Improved, Unchanged, and Worsened. The results of the AD score, hyperemia score, and patient questionnaire were scored in three grades: +1 for Improved, 0 for Unchanged, and −1 for Worsened. The scores were evaluated using Wilcoxon signed-rank tests. Data were statistically analyzed using JMP ver. 10.0.2 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patient Background

Of 30 patients who provided informed consent, 28 entered the fixed-combination

phase; two patients were excluded owing to discontinuation of treatment during the concomitant phase (adverse event or consent withdrawal). All 28 patients comprised the safety analysis set, of which 24 patients (excluding four: violation of protocol; use of gel-forming timolol in the morning of the first day of Week 0) were included in the efficacy analysis set (Table 1). The 28 patients in the safety analysis set comprised 11 men (39.3%) and 17 women (60.7%); these patients exhibited the following forms of glaucoma: NTG (16, 57.1%), POAG (11, 39.3%), and OH (one, 3.6%). Eight patients (28.6%) experienced ocular complications at Week −4. The 24 patients in the efficacy analysis set consisted of eight men (33.3%) and 16 women (66.7%); these patients exhibited the following forms of glaucoma: NTG (14, 58.3%), POAG (nine, 37.5%), and OH (one, 4.2%). Six patients (25.0%) experienced ocular complications at Week −4. Dorzolamide hydrochloride ophthalmic solution, a brinzolamide ophthalmic suspension, a brimonidine tartrate ophthalmic solution, and a bunazosin hydrochloride ophthalmic solution (Table 1) were used concomitantly with tafluprost and gel-forming timolol for glaucoma treatment.

3.2. Adherence Rate

Adherence rate was ≥80% throughout the study period (Figure 2). At Week −4,

Table 1. Patient background.

Analysis set (n)	Safety analysis set (28)	Efficacy analysis set (24)
Diagnosis, n (%)		
NTG	16 (57.1%)	14 (58.3%)
POAG	11 (39.3%)	9 (37.5%)
OH	1 (3.6%)	1 (4.2%)
Sex, n (%)		
Male	11 (39.3%)	8 (33.3%)
Female	17 (60.7%)	16 (66.7%)
Age (year)		
Minimum-Maximum	41.0 - 84.0	41.0 - 84.0
Mean ± standard deviation	66.6 ± 13.1	65.7 ± 13.6
Ocular complication, n (%)		
Positive	8 (28.6%)	6 (25.0%)
Negative	20 (71.4%)	18 (75.0%)
Concomitant glaucoma ophthalmic solution, n (%)		
Dorzolamide	4 (14.3%)	4 (16.7%)
Brinzolamide	17 (60.7%)	14 (58.3%)
Brimonidine	6 (21.4%)	5 (20.8%)
Bunazosin	1 (3.6%)	1 (4.2%)

Values are shown as number (frequency). Abbreviations: NTG; normal-tension glaucoma, OH; ocular hypertension, POAG; primary open-angle glaucoma.

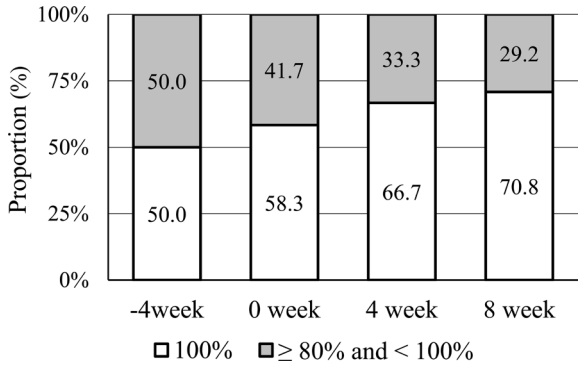

Figure 2. Changes in adherence rate. Adherence rate was evaluated by interview at each visit using a four-grade rating system: 1) 100%, 2) ≥80% and <100%, 3) ≥60% and <80%, and 4) <60%.

half of the patients reported 100% adherence; the remaining patients reported adherence between ≥80% and <100% range. The proportion of patients who reported 100% adherence increased gradually, such that it reached 70.8% at Week 8. However, no definite changes in adherence were noted between before and after switching (Weeks 0 and 4).

3.3. Intraocular Pressure

IOP data for the entire study period are shown in **Figure 3**. The mean IOP measurements in the efficacy analysis set were 14.8 ± 4.3, 14.2 ± 4.6, and 13.4 ± 4.3 mmHg (mean ± standard deviation) at Weeks 0, 4, and 8, respectively; notably, IOP was significantly decreased at Week 4 ($P = 0.054$) and Week 8 ($P = 0.0001$), compared with IOP at Week 0. Between Week −4 and Week 0, IOP did not change significantly ($P = 0.72$) (**Figure 3(a)**). The numbers of patients with an IOP reduction of ≥ 2 mmHg, compared with IOP at Week 0, were five (20.8%) at Week 4 and 10 (41.7%) at Week 8. In contrast, IOP increased by ≥ 2 mmHg in one patient (4.2%) at Week 4, compared with IOP at Week 0 (**Figure 3(b)**).

3.4. Ocular Surface Safety

The AD score for the severity of corneal epithelial disorders [15] was A0D0 or A1D1 in many patients throughout the study period (**Figure 4(a)**); changes in AD score are shown in **Table 2**. The AD score at Week 4 was significantly improved, compared with the score at Week 0 ($P = 0.0156$, Wilcoxon signed-rank test); however, AD score at Week 8 was not changed, compared with the score at Week 0 ($P = 0.7266$). At Week 4, seven patients (25.0%) experienced an improvement in AD score, while the remaining 21 patients (75.0%) did not show changes. At Week 8, five patients (18.5%) experienced an improvement in AD score, while three patients (11.1%) experienced an aggravation. Likewise, the conjunctival hyperemia score was 0 or 1 in many patients throughout the study period (**Figure 4(b)**); changes in hyperemia score are shown in **Table 3**. The hyperemia score did not change at either Week 4 or Week 8, compared with the

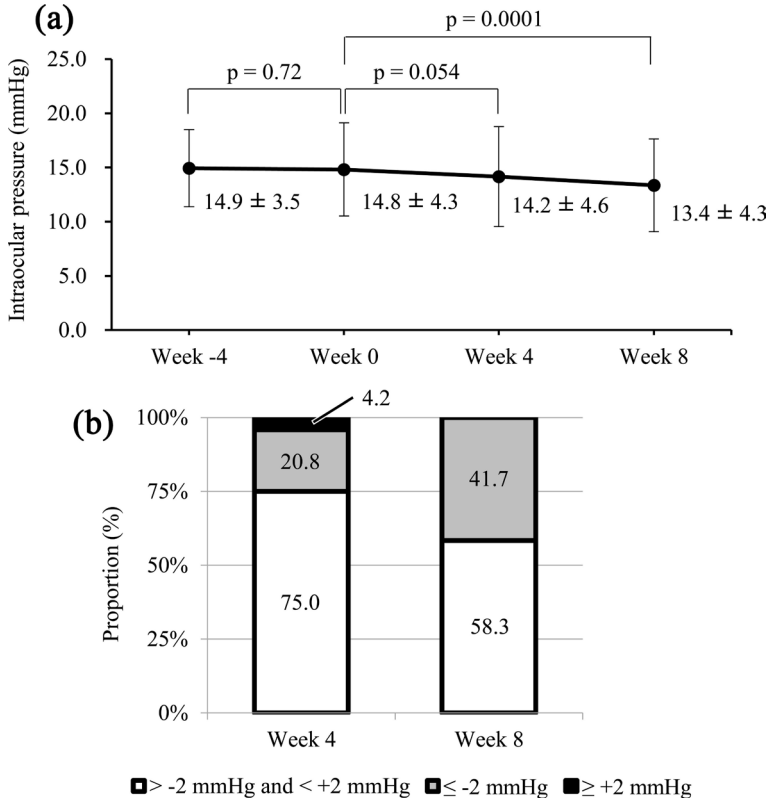

Figure 3. Changes in intraocular pressure. Intraocular pressure (IOP) (mean ± standard deviation) was measured at each visit. a) IOP changes between Weeks 0 and −4, Weeks 0 and 4, and Weeks 0 and 8 were evaluated by using paired *t*-tests. b) The proportion of patients with IOP changes ± ≥2 mmHg.

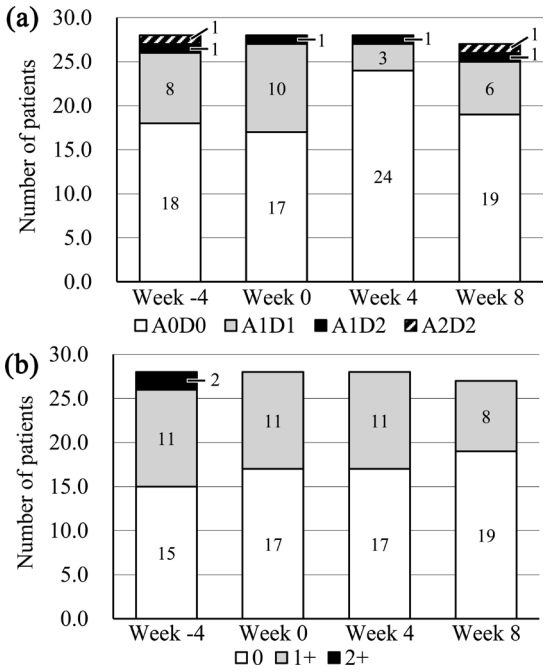

Figure 4. Ocular surface safety. Ocular surface safety profile was evaluated at each visit. The numbers of patients categorized by (a) area density classification score of corneal epithelial disorder and (b) hyperemia score are shown.

Table 2. Changes in area density classification score.

	Change	N	%	*P* value
Week 0 to Week 4	Improved	7	25.0%	0.0156
	Unchanged	21	75.0%	
	Aggravated	0	0.0%	
Week 0 to Week 8	Improved	5	18.5%	0.7266
	Unchanged	19	70.4%	
	Aggravated	3	11.1%	

Changes in area density classification score of corneal epithelial disorder were categorized into three grades using total area + density score and evaluated using Wilcoxon signed-rank tests.

Table 3. Changes in hyperemia score.

	Change	N	%	*P* value
Week 0 to Week 4	Improved	2	7.1%	1
	Unchanged	24	85.7%	
	Aggravated	2	7.1%	
Week 0 to Week 8	Improved	3	11.1%	0.625
	Unchanged	23	85.2%	
	Aggravated	1	3.7%	

Changes in hyperemia score were categorized into three grades and evaluated using Wilcoxon signed-rank tests.

score at Week 0 ($P = 1$ and $P = 0.625$, respectively). At Week 4, two patients (7.1%) experienced an improvement in hyperemia score, while two patients (7.1%) experienced an aggravation in hyperemia score; the remaining 24 patients (85.7%) did not show changes. At Week 8, three patients (11.1%) experienced an improvement in hyperemia score, while one patient (3.7%) experienced an aggravation in hyperemia score; the remaining 23 patients (85.2%) did not show changes.

3.5. Patient Questionnaire Regarding Usability of Ophthalmic Solution

Figure 5 shows the results of a patient questionnaire, administered at Week 8 in safety analysis set, regarding changes in the usability of ophthalmic solution before and after switching to TTFC. Regarding the frequency of forgetting to perform instillations associated with switching to TTFC, 17 patients (60.7%) responded with "Unchanged," and the remaining 11 patients (39.3%) responded with "Decreased"; this indicated a significant improvement in patient perception of adherence ($P = 0.001$). In terms of the usability of the container for instillation, 16 patients (57.1%) responded with "Unchanged," 11 patients (39.3%) with "Improved," and one patient (3.6%) with "Worsened"; this indicated a significant improvement in usability ($P = 0.006$). In terms of instillation comfort, 20

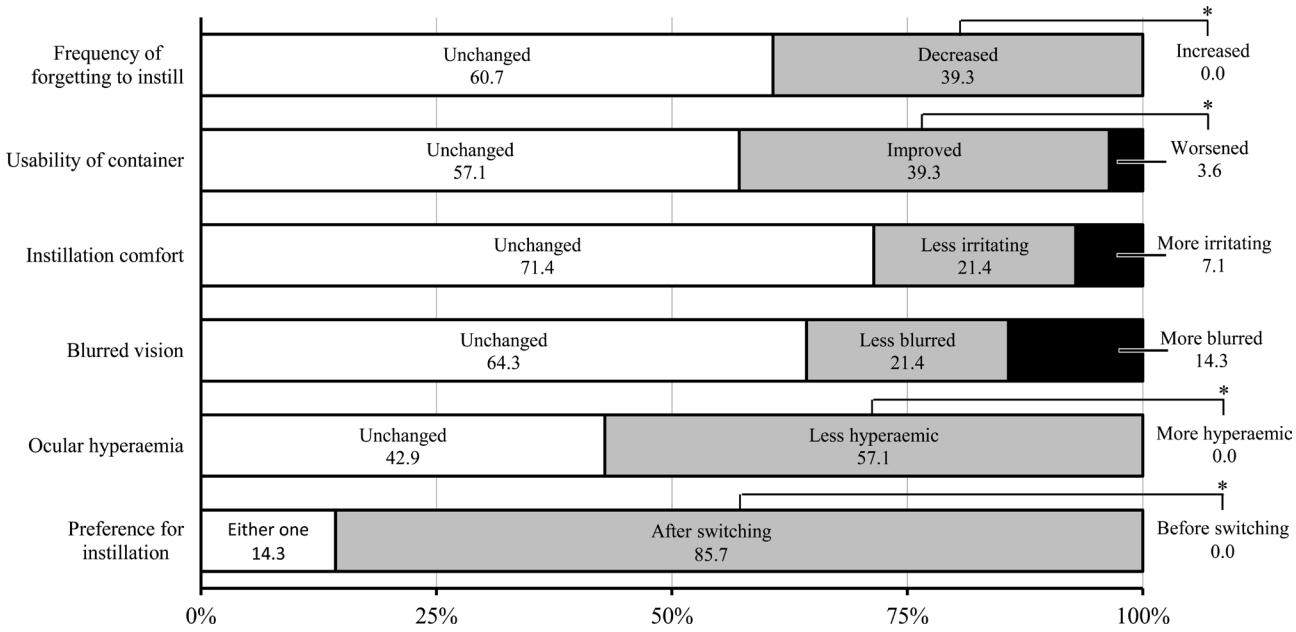

Figure 5. Patient questionnaire regarding the usability of ophthalmic solution. Patient questionnaire regarding the usability of tafluprost/timolol fixed-combination, compared with before switching, was administered at Week 8. The changes were scored in three grades and evaluated using Wilcoxon signed-rank tests. $P < 0.05$ was considered to be statistically significant. *$P < 0.05$.

patients (71.4%) responded with "Unchanged," six patients (21.4%) with "Less irritating," and two patients (7.1%) with "More irritating"; this indicated no significant difference in instillation comfort ($P = 0.289$). In addition, regarding blurred vision, 18 patients (64.3%) responded with "Unchanged," six patients (21.4%) with "Less blurred," and four patients (14.3%) with "More blurred"; this indicated no significant difference in blurred vision ($P = 0.754$). Regarding ocular hyperemia, 12 patients (42.9%) responded with "Unchanged," and the remaining 16 patients (57.1%) with "Less hyperemic"; this indicated a significant difference in patient perception of hyperemia ($P < 0.0001$). Finally, regarding patient preference for instillation, four patients (14.3%) responded with "No preference," and the remaining 24 patients (85.7%) with "A combination including the fixed-combination drug is preferred"; this indicated a significant difference in patient preference for instillation ($P < 0.0001$).

3.6. Adverse Events

Among the 28 patients who entered the fixed-combination phase, adverse events were reported in two patients within the period from Week 0 to Week 8. In both patients, a relationship with the study drug was ruled out, and resolution or recovery was reported. Of these two patients, one experienced an exacerbation of allergic conjunctivitis at Week 8 and was excluded from the Week 8 evaluation of ocular surface safety, but was included in the efficacy analysis set.

4. Discussion

In the present hospital-based multi-center study, we investigated changes in IOP

in glaucoma patients undergoing multi-drug therapy, caused by switching from concomitant use of tafluprost and gel-forming timolol to TTFC. In addition, adherence, ocular surface safety, and the usability of ophthalmic solutions were compared before and after switching. In a prior switching study by Inoue et al., involving switch to TTFC from concomitant use of tafluprost and gel-forming timolol solution, IOP was not changed after switching; [16] although that study design was similar to ours, the results differed. The reason for this difference is currently unclear; however, the prior study was conducted in a single clinic, whereas our study was conducted in multiple university hospitals and major hospitals throughout a particular region. Patients of the clinic and hospital may exhibit some differences, such as disease status (more progressed or more progressive in the hospital) and patient care; these differences may be related to the differences between in our study results and in the previous study results.

As a result of switching from concomitant use of tafluprost and gel-forming timolol to TTFC, IOP at Week 8 after switching decreased significantly, compared with IOP at Week 0 (**Figure 3(a)**). There are some possible reasons for the increased IOP-lowering effect observed upon switching to TTFC. First, improved adherence owing to the reduced number of medication bottles may increase the IOP-lowering effect. However, because the adherence rate remained high and did not show clear change between before and after switching (**Figure 2**), there may have been minimal influence of altered adherence on IOP reduction in the present study. Second, change in the usability of the container may have influenced the IOP-lowering effect. In instillation treatment, the ophthalmic solution must enter the eye; this is likely to be influenced by the usability of the container. The patient questionnaire showed that approximately 40% of the patients responded with "the container after switching was easier to instill"; therefore, the IOP may have been lowered as a result of the increased instillation success rates, due to improved ease of instillation. However, this hypothesis could not be investigated because instillation success rates were not assessed in the present study. Third, the IOP may have been lowered as the washout effect decreased, owing to the reduced number of concomitant drops that were instilled. In the present study, another glaucoma ophthalmic solution for b.i.d. or t.i.d. instillation was used concomitantly. Therefore, the washout effect between the gel-forming timolol (instilled in the morning) and the third drug may have been avoided by switching to TTFC (**Figure 1**). However, the extent of the influence could not be analyzed because the present study did not investigate instillation time, instillation intervals, or any related parameters. Fourth, the IOP-lowering effect may have been influenced by differences in the formulation of the ophthalmic solution. Pharmacokinetic analysis of TTFC showed higher aqueous timolol concentrations after 12 hours following the instillation of TTFC, compared with those present following instillation of gel-forming timolol [17]. Hence, IOP may have been lowered owing to differences in timolol transferability. It should be noted that these pharmacokinetic data were obtained in a

pre-clinical study; thus, it remains unknown how IOP reduction is influenced in humans.

An advantage of switching to TTFC is that exposure to preservatives decreases as the number of medication bottles is reduced. In the present study, ocular surface safety was expected to improve, as the number of medication bottles decreased from three to two upon switching to TTFC. However, a significant improvement in AD score was noted only between Week 0 and Week 4 in a small group of patients. Similarly, there were no significant changes in hyperemia scores. These results suggest that there was no difference in ocular surface safety, between before and after switching, in the present study. This may be because of the high likelihood that score reductions after switching to TTFC may be difficult to detect because the baseline AD and hyperemia scores were low.

In terms of frequency of forgetting to perform ophthalmic solution instillations, 39.4% of patients responded with "Decreased" (**Figure 5**); notably, this change could be the result of the reduced number of medication bottles (decreased from three to two). However, it should be noted that this response may not accurately reflect reality, because the study population exhibited ≥ 80% adherence rate throughout the study period and did not show a definite change between before and after switching (**Figure 2**). Regarding the usability of the container for instillation, 39.3% of patients responded with "Improved," and 3.6% of patients responded with "Worsened." The difference in the container used for TTFC and gel-forming timolol could explain this result. Adherence may be affected by the difficulty of instillation; thus, a container that facilitates instillation is an important aspect for drug choice. Regarding instillation comfort and blurred vision, no significant tendencies were found; 71.4% and 64.3% of patients responded with "Unchanged," respectively. This may be because of the absence of major changes in formulation composition and characteristics, between before and after switching. Regarding hyperemia, 57.1% of patients responded with "the fixed-combination drug was less likely to cause hyperemia," despite the absence of changes in physician-assessed hyperemia score between before and after switching. This discrepancy may be explained by differences in hyperemia rating criteria between the physician's assessment and the patient's subjective assessment. Finally, the patient preference for instillations revealed that a significantly greater percentage of patients preferred the fixed-combination drug, compared with concomitant use. This may be attributed to the reduced frequency of instillation and the improved usability of the container. Selection of a drug preferred by the patient is likely to result in improved adherence and may thus ensure a better therapeutic effect; therefore, TTFC may be a useful option for multi-drug therapy for glaucoma patients.

This study had some limitations. First, it was an open-label switching study; therefore, some biases could not be ruled out. Second, because adherence rate was periodically checked at 4-week intervals in the present study, the recorded data may be influenced by the fact that adherence may improve immediately

prior to visits (white coat effect). [18] [19] Third, because both the adherence survey and patient questionnaire were based on self-reporting by patients, the data obtained may not reflect objective findings of actual adherence. Using an objective survey method, for example, with equipment that electronically records instillation times and actions, is preferable for enabling an extensive investigation of the relationship between adherence or washout effect and IOP reduction.

5. Conclusion

In conclusion, TTFC showed greater IOP reduction than concomitant therapy. Thus, TTFC may be a better option in glaucoma patients than concomitant therapy.

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Conflicts of Interest

K.M., M.K., & N.S. have received financial support from Santen Pharmaceutical Co. Ltd., Kowa Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Nikon Healthcare Japan Inc., HOYA Corporation, Alcon Japan Ltd., Alcon Pharma, Senju Pharmaceutical Co., Ltd., Ogura Inc., Pfizer Japan Inc. and M.K. has received financial support from Iwaki & Co. Ltd.

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K.M. has received consulting fee from Santen Pharmaceutical Co., Ltd. and Kowa Pharmaceutical Co., Ltd.

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