Preservative-Free Fixed Combination of Tafluprost 0.0015% and Timolol 0.5% for Treatment-Naive Patients with Open-Angle Glaucoma

Teakkwan Rhee, MD¹, Jaeheon Kim, MD²,³, Ahnul Ha, MD²,³

¹ Yonsei Jeil Eye Clinic, Jeju-si, Korea
² Department of Ophthalmology, Jeju National University Hospital, Jeju-si, Korea
³ Department of Ophthalmology, Jeju National University School of Medicine, Jeju-si, Korea

Corresponding author: Ahnul Ha, MD

Department of Ophthalmology, Jeju National University Hospital, Jeju National University School of Medicine, 15, Aran 13-gil, Jeju-si, Jeju-do, 61241, Republic of Korea
Tel: 82-64-717-2064; Fax: 82-2-64-717-8276
E-mail: zzammy486@gmail.com

Running title: PF Tafluprost/Timolol in Treatment-Naive Glaucoma
Abstract

**Purpose:** To assess efficacy, safety, and tolerability of the preservative-free fixed-dose combination of tafluprost 0.0015%/timolol 0.5% (PF tafluprost/timolol FC) in treatment-naïve patients with primary open-angle glaucoma (POAG).

**Methods:** This was a retrospective, real-world clinical practice setting study that included 107 eyes of 107 subjects with POAG who had never been treated for glaucoma. All subjects were received PF tafluprost/timolol FC once daily. Intraocular pressure (IOP) levels were documented for each eye at the untreated baseline and up to six months after the initiation of medical treatment. All adverse events, including ocular and systemic adverse reactions, were recorded. Additionally, the reasons for medication discontinuations were thoroughly documented.

**Results:** A total of 32 POAG patients with high-baseline IOP (>21 mmHg) and 75 with normal-baseline IOP were included in the study. The subjects’ baseline mean age was 62.4 ± 8.7 (range: 26–85 years); among them, 42 were women (39.3%). Mean IOP at baseline for all patients was 18.6 ± 4.3 mmHg. The mean IOP at six months was 12.6 ± 4.7 mmHg, representing a significant decrease compared to the baseline (-32%; *P* < 0.001). In POAG patients with high-baseline IOP, mean IOP was significantly lowered from 28.0 ± 5.7 mmHg at baseline to 18.0 ± 5.5 mmHg (-35%; *P* < 0.001); in patients with normal-baseline IOP, from 14.6 ± 3.4 mmHg to 10.3 ± 4.1 mmHg (-29%; *P* < 0.001). PF tafluprost/timolol FC was well tolerated and safe. After 6 months, 97.2% of all patients remained on therapy.

**Conclusions:** In this real-world observational study, once-daily treatment with PF tafluprost/timolol FC demonstrated clinically relevant and statistically significant efficacy, as well as safety and good tolerability, in treatment-naïve patients diagnosed with POAG.

**Keywords:** Adverse effects, Anti-glaucoma agents, Intraocular pressure, Primary open-angle glaucoma
INTRODUCTION

The preservative-free (PF) fixed-dose combination (FC) of 0.0015% tafluprost and 0.5% timolol (PF tafluprost/timolol FC; Santen Oy, Tampere, Finland) has been accessible in Korea since 2020. It is primarily indicated for reducing intraocular pressure (IOP) in adult patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) who exhibit insufficient responsiveness to topical monotherapy with beta-blockers or prostaglandin analogs (PGAs) [1]. Therefore, this combination therapy, PF tafluprost/timolol FC, is recommended for individuals in need of multiple IOP lowering medications and who would derive advantages from PF eye drops.

Medical treatment in OAG or OHT usually starts with a single topical hypotensive agent, a practice supported not only by the European Glaucoma Society but also by many other guidelines [2-4]. However, monotherapy might prove inadequate in numerous patients, as it may not achieve the target pressure and/or prevent glaucoma progression effectively [5]. In clinical practice, as a result, FC drugs are frequently chosen as the primary treatment for a considerable number of patients [6], especially in cases where the baseline IOP is exceedingly high and/or when glaucoma has already advanced considerably.

Issues related to local toxicity arising from exposure to preservative agents, including the widely used benzalkonium chloride, can impact treatment adherence and result in inadequate IOP control [7-9]. Ocular surface disease is more common in individuals with glaucoma compared to the general population [10, 11], and the application of topical medications containing preservatives may worsen inflammation, leading to suboptimal long-term therapeutic and surgical results as well as diminished quality of life [12-14]. Consequently, there is an increasing trend in the utilization of PF topical medications for glaucoma management [15].

There have been limited studies specifically evaluating the efficacy and safety of PF tafluprost/timolol FC in treatment-naive patients. This observational study aimed to assess the effectiveness in lowering IOP, as well as the tolerability and safety, of the PF tafluprost/timolol FC solution in real-world clinical practice settings. The evaluation was conducted on treatment-naive Korean patients diagnosed with primary open-angle glaucoma (POAG), including individuals with normal baseline IOP.

MATERIALS AND METHODS

Ethics statement

The institutional review board of Jeju National University Hospital approved (2024-01-010) this retrospective study, which adhered faithfully to the tenets of the Declaration of Helsinki. Informed consent was waived due to
the study's retrospective nature.

Study subjects

Patient data were extracted from the Jeju National University Hospital Clinical Data Warehouse (CDW), covering the period from January 2021 to September 2023. The electronic medical records retrospectively reviewed in this study belonged to POAG patients who had never been treated for glaucoma and had attended regular check-ups at the Jeju National University Hospital’s glaucoma clinic. The initiation of medical treatment was determined by a sole glaucoma specialist. Patients with contraindications (e.g., diagnosed with asthma or arrhythmia) were excluded in accordance with the summary of product characteristics for PF tafluprost/timolol FC [1].

All of the subjects underwent a complete ophthalmic examination, including a best-corrected visual acuity assessment, refraction, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland), and dilated stereoscopic optic disc examination. Additionally, central corneal thickness measurements (Orbscan 73 II; Bausch & Lomb, Rochester, NY, USA), stereo disc photography, red-free retinal nerve fiber layer photography, Cirrus HD-OCT imaging (Carl Zeiss Meditec, Dublin, CA, USA), and central 24-2 threshold testing via the Humphrey visual field (VF) analyzer (HFA II; Humphrey Instruments, Dublin, CA, USA) were undertaken.

The diagnosis of POAG was based on the appearance of the optic disc (localized or diffuse neuroretinal rim thinning/notching) on stereo disc photography with retinal nerve fiber layer defect in the corresponding region (based on red-free fundus imaging), an open angle as confirmed by gonioscopic examination, and the presence of glaucomatous VF defect. Glaucomatous VF defects were defined as follows: (1) a cluster of three points having probabilities of less than 5% in at least one hemifield on a pattern deviation map, including at least one point having a probability of less than 1% or a cluster of two points having a probability of less than 1%; (2) glaucomatous hemifield test results that were outside the normal limits; and (3) a pattern standard deviation of more than 95% of the normal limits, as confirmed by at least two reliable examinations (false-positives/negatives < 15%, fixation losses < 15%). If both eyes of a single patient were eligible, one was chosen randomly.

Measurement of IOP

Goldmann applanation tonometry was used to measure IOP at baseline and during every follow-up visit thereafter. The collected IOP measurements were compared between the baseline and one, six months after the
treatment initiation.

Assessments of adverse drug reactions

The identification of bulbar conjunctival hyperemia relied on reference images, specifically utilizing the grading scales from the Cornea and Contact Lens Research Unit [16]. Diagnosis of allergic conjunctivitis associated with anti-glaucoma medications relied on clinical symptoms and signs, encompassing pruritus, conjunctival injection, follicular conjunctival reaction, contact dermatitis of the eyelids, or eyelid swelling. Additionally, subjective assessments provided by individual patients were used to identify other potential side effects, such as eye irritation, blurred vision, foreign body sensation, or eyelid pigmentation. Patients were queried about any potential systemic symptoms attributable to medication, including but not limited to palpitations, dizziness, syncope, cough, and dyspnea [17].

Statistical analysis

Longitudinal changes in IOP were examined by comparison between baseline and each interval value using the repeated-measures analysis of variance (ANOVA), accounting for the within-subject correlation of IOP data. Then, the extents of IOP change at different time points were compared using the paired t-test with Bonferroni correction. The bulbar conjunctival hyperemia grades before and after treatment initiation were analyzed using the Wilcoxon signed-rank test, considering that the data did not follow a normal distribution. Statistical analyses were performed using the IBM SPSS Statistics ver. 22.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value of less than 0.05 was considered to represent statistical significance.

RESULTS

Initially, among the 214 individuals who were first-time users of the anti-glaucoma medication PF tafluprost/timolol FC, after applying inclusion and exclusion criteria, a total of 107 participants were included in the final analysis. The subjects’ baseline mean age was 62.4 ± 8.7 (range: 26 – 85 years); among them, 65 were men (60.7%) and 42 women (39.3%). The untreated IOP was 18.6 ± 4.3 (range: 14 – 38 mmHg). The baseline demographics and clinical characteristics are presented in Table 1.

Efficacy
One month after initiation of medical therapy, IOP decreased significantly from 18.6 ± 4.3 mmHg to 12.8 ± 4.3 mmHg in overall patients. This IOP decrease is equivalent to 5.8 mmHg, or 31% versus untreated baseline. A significant decrease in mean IOP was achieved for different subgroups by diagnosis: in patients with POAG (n = 32), mean IOP (± SD) was significantly lowered from 28.0 ± 5.7 mmHg at baseline to 18.5 ± 5.2 mmHg at one month; in patients with NTG (n = 75), from 14.6 ± 3.4 mmHg to 10.4 ± 3.5 mmHg.

The IOP at six months was analyzed among 104 patients who had adhered to the medication up to that point. Overall, the mean IOP was 12.6 ± 4.7 mmHg, representing a significant decrease compared to the baseline (-32%). In patients with POAG (n = 31), mean IOP (± SD) was significantly lowered from 28.0 ± 5.7 mmHg at baseline to 18.0 ± 5.5 mmHg at six month; in patients with NTG (n = 73), from 14.6 ± 3.4 mmHg to 10.3 ± 4.1 mmHg.

Repeated-measures ANOVA revealed that IOP at baseline, one month after treatment initiation, and six months after treatment initiation differed across all patients, as well as in the POAG and NTG groups (all $P$s < 0.001). Further details on IOP lowering effect are shown in Table 2.

Safety

Few adverse events were associated with the use of PF tafluprost/timolol FC. A total of five patients (4.7%) complained of conjunctival hyperemia, and in the majority of cases (n = 4), the severity remained similar or improved while continuing the medication, making discontinuation unnecessary. The bulbar conjunctival hyperemia grades before and after treatment initiation were 2.13 ± 0.74 and 2.23 ± 0.78, respectively ($P = 0.056$). No patients reported systemic side effects.

During the 6-month observational period, a total of three patients (2.8%) discontinued PF tafluprost/timolol FC treatment. One patient discontinued medication use due to suspected signs of allergy accompanied by hyperemia, another due to periorbital fat atrophy and eyelid pigmentation, and a third due to the high cost of the medication. As is apparent, there were no serious ADRs encountered in this study.

DISCUSSION

In this retrospective, real-world setting study, PF tafluprost/timolol FC demonstrated both clinically relevant and statistically significant IOP reductions up to 6 months of usage in Korean patients with POAG. Notably, PF tafluprost/timolol FC was safe and well-tolerated.

In the literature, there are two pivotal randomized controlled trials (RCTs) investigating the efficacy of PF
tafluprost/timolol FC. Pfeiffer et al., in a study involving 564 patients, demonstrated the superior efficacy of PF tafluprost/timolol FC in individuals with OAG or OHT who had insufficiently controlled IOP with prior timolol or PGA monotherapy [18]. In the tafluprost stratum, PF tafluprost/timolol FC reduced IOP from baseline by 8.61 mmHg, corresponding to a 33% reduction in IOP. The treatment with PF tafluprost/timolol FC resulted in IOP reductions of 8.55 mmHg in the timolol stratum, indicating a 32% reduction from the baseline value. Holló et al. demonstrated that the IOP-lowering efficacy of PF tafluprost/timolol FC therapy was comparable to that of the separate PF tafluprost and timolol non-fixed combination, based on data from 400 patients [19]. The mean diurnal IOP reduction at 6 months was approximately 8.0 mmHg (-32%) with PF tafluprost/timolol FC therapy and 8.3 mmHg (-33%) with concurrently administered tafluprost and timolol.

In an open-label observational study, IOP reduction after 4–16 weeks of using PF tafluprost/timolol FC in treatment-naïve patients was investigated [20]. In a total of 128 treatment-naïve patients, the mean IOP decreased by approximately 8.9 mmHg, corresponding to a 34% reduction. Similarly, in our study, treatment-naïve patients initiated with PF tafluprost/timolol FC therapy showed an approximately 32% reduction in IOP at the 6-month mark. However, a noteworthy aspect in our study is the inclusion of a majority of POAG patients with a normal baseline IOP. Consequently, the baseline IOP was significantly lower (i.e., 18.6 mmHg) compared to previous studies. In the two above-mentioned RCTs [18, 19], the baseline IOP ranged from 24 to 27 mmHg, while the observational study, which included treatment-naïve patients, also had a baseline IOP of approximately 26 mmHg. Considering the difficulty in reaching the target pressure in patients with low baseline IOP [21], the observed IOP-lowering effect of PF tafluprost/timolol FC in this study among patients with relatively low baseline IOP is remarkable.

The lack of preservative agents in PF tafluprost/timolol FC contributes to enhanced tolerability, potentially leading to improved adherence and treatment compliance [22]. Additionally, incorporating timolol has been demonstrated to improve the tolerability of PGA agents in FC therapies [23]. In our results, we observed a low frequency of adverse reactions for PF tafluprost/timolol FC in treatment-naïve patients. Only two patients discontinued treatment due to local tolerability issues, and none of the patients reported systemic intolerance problems. Data from RCTs also indicated that 70–80% of patients did not report discomfort during the instillation of PF tafluprost/timolol FC [18, 19]. In an observational study involving 1157 patients, only 2.5% and 0.6% discontinued PF tafluprost/timolol FC treatment due to local and systemic adverse reactions, respectively [20].

There are several limitations to our study. First, as the study was conducted in the real-world setting, it was not possible to assess medication adherence, specifically how accurately and consistently patients were instilling the
medication. Therefore, the potential impact of individual patient adherence to medication on the amount of IOP reduction and the occurrence of side effects should be taken into consideration. Second, this study measured the baseline IOP only once, and due to the absence of a comparator group, regression to the mean cannot be ruled out [24]. Further well-controlled clinical studies are necessary to fully determine the efficacy of PF tafluprost/timolol FC in treatment-naive patients with POAG. Third, we implemented a relatively short-term, 6-month observational period. Medications, including PGA, may lead to prostaglandin-associated periorbitopathy, which tends to increase with prolonged use [25]. Consequently, the persistence rate of PF tafluprost/timolol FC may decrease over time. Further, a long-term observation is necessary to comprehensively assess the tolerability and safety of PF tafluprost/timolol FC.

In summary, the findings of the present study suggest that, within the context of routine clinical practice, PF tafluprost/timolol FC leads to both clinically and statistically significant reductions in IOP among treatment-naive POAG patients, including those with normal-baseline IOP. Additionally, PF tafluprost/timolol FC was well tolerated throughout the 6-month treatment period.

**Financial disclosure:**

No author has a financial or proprietary interest in any material or method mentioned.

**Conflicts of Interest:**

No conflicting relationship exists for any author.
REFERENCES


18. Pfeiffer N, Traverso CE, Lorenz K, et al. A 6-month study comparing efficacy, safety, and tolerability of the preservative-free fixed combination of tafluprost 0.0015% and timolol 0.5% versus each of its individual preservative-free components. *Adv Ther* 2014;31:1228-46.


20. Pillunat LE, Erb C, Ropo A, Kimmich F, Pfeiffer N. Preservative-free fixed combination of tafluprost 0.0015% and timolol 0.5% in patients with open-angle glaucoma and ocular hypertension: results of an open-label observational study. *Clin Ophthalmol* 2017:1051-64.


Table 1. Demographic characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.4 ± 8.7 (range: 26 to 85)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65 (60.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (39.3%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>POAG</td>
<td>32 (29.9%)</td>
</tr>
<tr>
<td>NTG</td>
<td>75 (70.1%)</td>
</tr>
<tr>
<td>Baseline IOP (mmHg)</td>
<td>18.6 ± 4.3 (range: 14 to 38)</td>
</tr>
<tr>
<td>Spherical equivalent (diopters)</td>
<td>-1.8 ± 2.8 (range: -5.6 to +2.0)</td>
</tr>
<tr>
<td>Central corneal thickness (µm)</td>
<td>531.5 ± 31.0 (range: 468 to 616)</td>
</tr>
<tr>
<td>Visual field MD (decibels)</td>
<td>-9.5 ± 4.8 (range: -27.1 to -2.8)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

IOP = intraocular pressure, MD = mean deviation.
Table 2. Change in mean intraocular pressure: baseline to 1 and 6 months after commencement of medical therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean IOP at baseline (mm Hg)</th>
<th># of eyes at 1 month</th>
<th>Mean IOP at 1 month (mm Hg)</th>
<th>% Reduction at 1 month</th>
<th>P value*</th>
<th># of eyes at 6 month</th>
<th>Mean IOP at 6 month (mm Hg)</th>
<th>% Reduction at 6 month</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>18.6 ± 4.3</td>
<td>107</td>
<td>12.8 ± 4.3</td>
<td>31</td>
<td>&lt; 0.001</td>
<td>104</td>
<td>12.6 ± 4.7</td>
<td>32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>POAG</td>
<td>28.0 ± 5.7</td>
<td>32</td>
<td>18.5 ± 5.2</td>
<td>34</td>
<td>&lt; 0.001</td>
<td>31</td>
<td>18.0 ± 5.5</td>
<td>35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NTG</td>
<td>14.6 ± 3.4</td>
<td>75</td>
<td>10.4 ± 3.5</td>
<td>29</td>
<td>&lt; 0.001</td>
<td>73</td>
<td>10.3 ± 4.1</td>
<td>29</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure, POAG = primary open-angle glaucoma, NTG = normal tension glaucoma.

*A paired t-test comparing the intraocular pressure levels between baseline and the 1-month follow-up.

†A paired t-test comparing the intraocular pressure levels between baseline and the 6-month follow-up.