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ORIGINAL RESEARCH

24-Hour Evaluation of the Effectiveness and Tolerability of Preservative-Free Tafluprost-Timolol Fixed Combination in Open-Angle Glaucoma or Ocular Hypertensive Patients Previously Treated with Preserved Latanoprost

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Purpose: The effectiveness, safety and tolerability of the preservative-free fixed combination of tafluprost and timolol (PF-TTFC) were evaluated over the 24-h in patients with open-angle glaucoma or ocular hypertension showing signs and symptoms of Ocular Surface Disease (OSD) and uncontrolled intraocular pressure (IOP) on prior benzalkonium chloride (BAK) – Latanoprost monotherapy.

Methods: In this multi-center, prospective, interventional, non-comparative clinical trial, patients treated with BAK-Latanoprost underwent 24-h IOP measurements (8 am, 11 am, 2 pm, 5 pm, 8 pm, 11 pm, 2 am, 5 am) at baseline and after 3 months from switch to PF-TTFC. Mean 24-h IOP and daytime (8 am–8 pm) vs nighttime (11 pm – 5 am) IOP were compared. Changes in OSD signs and symptoms, quality of life (QoL) and in-vivo corneal confocal microscopy (IVCM) were also evaluated.

Results: Thirty-eight patients were analyzed. The mean 24-h IOP significantly decreased after 3 months from 17.8 mmHg (95% CI: 17.1–18.6) to 15.3 mmHg (95% CI: 14.6–16.1, $p < 0.001$). IOP was significantly reduced both at daytime ($p < 0.001$) and nighttime ($p < 0.001$), with better IOP control at night [−2.9 (95% CI: −3.5 to −2.1) mmHg vs −2.3 (95% CI: −2.9 to −1.6) mmHg]. In 20 patients (52.6%), corneal fluorescein staining improved, whereas in 4 patients (10.5%) it worsened. Hyperemia has improved in 24 (63.3%) patients and worsened in 2 (5.3%). Breakup time, Schirmer test and QoL scores showed no changes. At IVCM, the mean corneal wing-cell size was found significantly decreased ($p < 0.005$).

Conclusion: The switch from BAK-Latanoprost to PF-TTFC significantly reduced IOP over the 24-h and improved OSD signs and symptoms.

Keywords: glaucoma, tafluprost-timolol fixed combination, preservative free, BAK, prostaglandins, 24-h effectiveness, ocular surface disease

Introduction

Lowering intraocular pressure (IOP) remains a mainstay of glaucoma treatment. Efficient ocular hypotensive combination therapies are expected to be effective in both reducing mean IOP and the IOP fluctuations over the 24 hours with the minimum number of drops and active compounds.

Despite ocular hypotensive medical therapy usually beginning with a topical monotherapy, often more than one agent is required to lower IOP to levels that allow to control progression of disease. Fixed combinations were introduced to enhance the overall efficiency of combination therapies by minimizing the number of daily administrations, improving adherence, enhancing tolerability, and ultimately improving the long-term outcome of therapeutical glaucoma management.[1] However, studies have

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shown that the higher the number of drops and the required daily administrations, the higher is the chance for the glaucoma patients to experience therapy-related ocular surface disease (OSD).[2–4] OSD is a constellation of disorders affecting the eyelids, conjunctiva, and/or the multilayered corneal surface. It more commonly affects the elderly population and according to prevalence studies, between 48% and 59% of patients with glaucoma or ocular hypertension (OHT) report symptoms of OSD in at least one eye.[2,3,5] Signs and symptoms include conjunctival and corneal epithelial damage, burning, redness, irritation, fatigue, fluctuating visual acuity, and infection with consequent decreased quality of life.[6] In addition to the number of medications, symptom severity is correlated with the use of preservatives in formulations, most commonly the benzalkonium chloride (BAK).[3–5] BAK is a detergent compound of polyquaternary ammonium that acts by lysing cell membranes,[7] thus exerting antimicrobial activity to maintain sterility.[8] However, BAK has also been shown to increase apoptosis and MMP-9 levels, likely implicated in glaucoma pathogenesis, as well as markers of oxidative stress, which may lead to stress-induced premature senescence of trabecular meshwork cells, characteristic of primary open-angle glaucoma.[9,10]

For these reasons, balancing the potential ocular surface-related side effects in patients needing a multidrug IOP-lowering treatment may be challenging. However, when treating BAK-sensitive patients who require the addition of another hypotensive agent, considering the use of preservative-free fixed combinations may improve not only the IOP control, as expected, but also the signs and symptoms of OSD caused by the treatment.[11]

The primary objective of the study is to evaluate the effectiveness in reducing the mean 24-hour IOP of the preservative-free fixed combination of tafluprost 0.0015% and timolol 0.5% (PF-TTFC) administered once at night in open-angle glaucoma (OAG) or OHT patients suffering at least a slight degree of OSD and requiring further IOP reduction while in topical treatment with BAK-Latanoprost 0.05 mg/mL. In addition, we evaluated the changes in signs, symptoms, and quality of life related to OSD.

Methods

This was a Phase IV multi-center, prospective, interventional, non-comparative clinical trial (registered with EudraCT number: 2019–003426-24 and available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003426-24/IT) that was carried out between June 2020 and May 2022.

Patients were recruited by 2 Italian centers (IRCCS Fondazione Bietti, Rome Italy; University of Milan, San Paolo Hospital, Milan, Italy). The study protocol was approved by the ethics committee at each center involved. The study complied with the principles of the Declaration of Helsinki and all patients included provided written informed consent prior to their enrollment.

Participants

Adult participants (age ≥18 years) were considered eligible according to the following criteria: (I) Diagnosis of OHT or Primary OAG or OAG secondary to dispersion of pigment or pseudoexfoliation, according to the definitions reported by the 5th ed. of the European Glaucoma Society Guidelines;[12] (V) Treatment with BAK-Latanoprost 0.05 mg/mL for at least 6 weeks before the enrollment; (II) IOP <22 mmHg in therapy with BAK-Latanoprost 0.05 mg/mL in both eyes and >17 mmHg in at least one eye; (III) OSD at least mild as defined by the 5-Item Dry Eye Questionnaire (DEQ-5) (score > 6).[13]

Exclusion criteria comprised other forms of glaucoma (including chronic or acute angle closure glaucoma), history of trabeculoplasty or glaucoma, cataract, corneal/refractive surgery in the 6 months prior to enrollment, BCVA <2/10 and visual field mean deviation (MD) <-20 dB, use of steroids, non-steroidal anti-inflammatory drugs, immunosuppressants or tear substitutes containing preservatives within 30 days prior to enrollment, corneal anomalies that preclude an accurate measurement of IOP (eg astigmatism >3 D, keratoconus, corneal opacity or ulcers), inability to understand and sign informed consent or to adhere to the procedures required by the protocol or to the studio treatment, hypersensitivity to the active substances or to any of the excipients.

Patients who had contraindications to the use of beta-blockers according to the approved licensed indications and product characteristics as well as women of childbearing potential, or who were currently pregnant or breastfeeding, were not considered eligible for this study.

Study Timepoints and Procedures

A summary of the study timepoints and procedures is depicted in Figure 1.

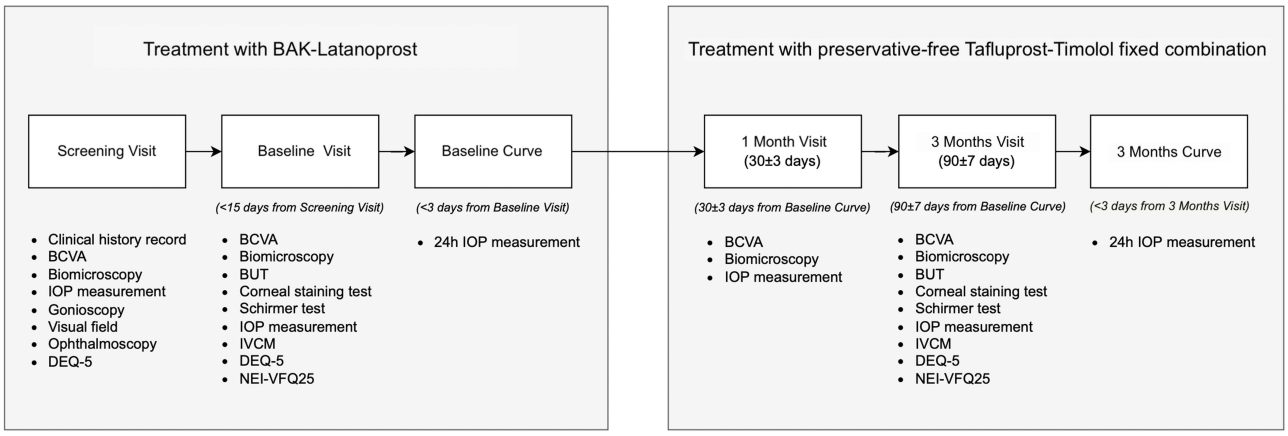

Figure 1 Study protocol.
Abbreviation: BAK, benzalkonium chloride; BCVA, Best Corrected Visual Acuity; IOP, Intraocular Pressure; DEQ-5, 5-Item Dry Eye Questionnaire; BUT, Break-up Time; IVCM, In vivo confocal microscopy; NEI-VFQ25, 25-item National Eye Institute Visual Function Questionnaire.

At the screening visit, eligibility criteria were evaluated by a comprehensive clinical exam (including BCVA in decimals, slit-lamp examination, and ophthalmoscopy) and a detailed assessment of systemic and ocular history. Visual field was tested with standard automated perimetry (24–2 SITA Standard program of the Humphrey Field Analyser, Carl Zeiss) and the irido-corneal angle was assessed by gonioscopy, performed with Goldmann 3 Mirror lens.

For all the IOP measurements, a dedicated and calibrated Goldmann applanation tonometer was used by a single trained investigator in each study center. The mean of two readings (or the median of three readings in case of >2 mmHg difference) was recorded. During the baseline and the 3 months (3M) visits, IOP was measured at 8 am, 11 am, 2 pm, 5 pm, 8 pm (in sitting position with Goldmann applanation tonometer) and 11 pm, 2 am, 5 am (in supine position with Perkins applanation tonometer).

Corneal and ocular surface were evaluated with Break-up time, Schirmer test I, and Corneal Staining test with fluorescein (reported using the Oxford grading scale from 0 to V grade, according to the intensity of corneal and conjunctival punctate staining).[14] Conjunctival hyperemia was graded from 0 (none) to 4 (severe).[14]

Symptoms of OSD were assessed using DEQ-5 at screening visit, baseline visit, and 3M Visit, whereas quality of life was measured with the validated Italian version of the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ25)[15] at Baseline and 3M Visit.

In vivo confocal microscopy (IVCM) was performed with Heidelberg Retinal Tomograph III equipped with Rostock Cornea Module (HRT III-RCM, Heidelberg Engineering). Patients were imaged at Baseline Visit and 3M Visit. A trained operator per center acquired multiple 30° × 20° scans and the best quality scan were chosen. A software for automatic segmentation of the confocal images acquired was used to obtain the mean count and length of corneal nerves and mean count, density and length of wing cells and dendritic immune cells in a region of interest of 0.1589 mm^2. The same trained operator checked the images and manually corrected the automatic segmentation and cell identification if required.

Any adverse events (AE) were recorded at each study visits excluding the screening visit.

Study Treatments

At the end of the Baseline Curve, the patients were asked to discontinue treatment with BAK-Latanoprost and to start the treatment period with preservative-free fixed combination of tafluprost 0.0015% and timolol 0.5%. The drug was provided by the study staff in a single-dose container (0.3 mL), and the patients were instructed to take one drop in the evening (at 8 pm).

Study Endpoints

The primary endpoint was the mean 24-h absolute IOP reduction after 3 months of treatment with PF-TTFC, compared to the 24-h absolute IOP at baseline obtained with BAK-Latanoprost.

Secondary endpoints were the reduction of IOP at each time of the 24-hour curve and daytime (8 am – 8 pm) and nighttime (11 am – 5 am) reduction of the IOP.

Mean changes in corneal and OSD clinical signs and symptoms (including Oxford grading scale scores, Schirmer test, BUT and DEQ-5 scores) and changes in mean scores of NEI-VFQ25 were also evaluated.

Additionally, corneal nerves' mean length and mean density, wing cells' mean count, density and average size and dendritic immune cells' mean count, density, and length at baseline and at 3M were compared.

Statistical Analysis

If only one eye was eligible, only the eye with the highest mean 24h IOP at the baseline curve was included in the statistical analysis, but both eyes were treated with the study medication. In the case of unilateral open-angle glaucoma or OHT, the patient was treated with the study medication only in the affected eye, continuing without therapy in the healthy eye (if both eyes were eligible, both were treated). If both eyes were eligible, only the eye with the highest average 24h IOP at the Baseline Curve was included in the statistical analysis.

Demographic and ocular characteristics of the patients enrolled have been described as median and interquartile ranges for continuous variables and frequencies for categorical variables.

The analysis of the primary outcome was performed using a mixed effect model with random effect on the intercept for each patient. IOP was used as a dependent variable in the model and the 24-h time points were considered as a fixed effect. The model was used to calculate the effect of the treatment on the single time-points and on the mean of the 24-h IOP. Similarly, mixed effect models were used to test the effect of the new therapy on signs and symptoms related to OSD, IVCM variables and QoL. The Bonferroni-Holm correction was used to perform pairwise comparisons.

The analysis was conducted in R (version 4.2.2)[16] with the lme4[17] and the lsmeans[18] packages. A P value of <0.05 was considered statistically significant.

Results

Forty-two patients were screened, and two patients were considered as screening failures. Among the 40 patients enrolled, 1 patient withdrew the consent before Baseline Curve and 1 patient before 3M Curve for personal reasons. A total of 38 patients finished the study. Table 1 summarises the characteristics of the study patients. Among open-angle glaucoma patients, 3 had pseudoexfoliative glaucoma.

The estimated mean 24-h IOP significantly decreased from 17.8 mmHg (95% CI: 17.1–18.6; coefficient of variation: 0.15) at baseline, to 15.3 mmHg (95% CI 14.6–16.1; coefficient of variation: 0.18). Three months after therapy switch from BAK-Latanoprost to PF-TTFC, the mean 24-h IOP reduction was 2.5 mmHg (95% CI: 2.0–2.9) ($p < 0.001$) corresponding to −14%. Statistically significant mean 24-h IOP reduction was also recorded at each timepoint (Figure 2 and Supplementary Table 1).

Table 1 Patients' Demographical and Clinical Characteristics at Baseline Visit

	Mean (SD)
Age, years	63.6 (11.6)
Gender [nF/nM]*	18/20
Noht/nGlaucoma*	14/24
BCVA, logMAR	0.1 (0.3)
MD, dB	−3.3 (5,6)
PSD, dB	3.7 (3.7)
IOP, mmHg	17.8 (1.37)
C/D Ratio	0.5 (0.2)

Abbreviations: OHT, Ocular Hypertension; BCVA, Best Corrected Visual Acuity; MD, Mean Deviation; PSD, Pattern Standard Deviation; IOP, Intraocular Pressure; C/D, Cup-to-Disc Ratio.

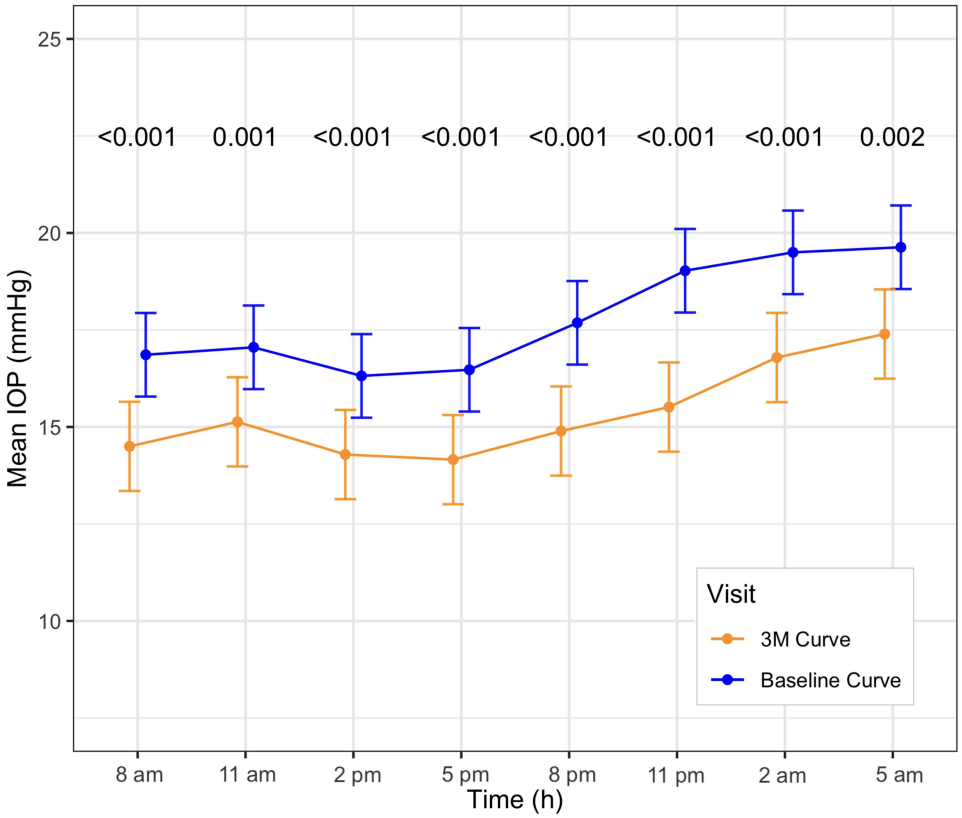

Figure 2 Intraocular pressure at each time point of the 24-h curve at Baseline and at 3 Months. Error bars represents standard deviation; p values for timepoint comparisons are reported.
Abbreviation: IOP, Intraocular pressure; 3M, 3 Months.

The highest percentage of 24-h IOP reduction was recorded at 11 pm with −3.5 mmHg (95% CI: 2.1–4.9) and corresponding to −18.4%, whereas the lowest was at 11 am with −1.92 mmHg (95% CI: 0.81–3.03) and corresponding to −11.2%.

The 24-h IOP curves were similar in shape before and after treatment with PF-TTFC (Figure 2), with IOP measured at night being considerably higher than IOP observed during the day ($p < 0.001$, Supplementary Table 2). However, the nocturnal IOP increase was greater during the Baseline Curve than it was over the 3M Curve, being +2.5 (95% CI: +1.8 – +3.1) mmHg (+14.8%) and +1.9 (95% CI: +1.3 – +2.5) mmHg (+13.0%), respectively. In addition, during the 3M Curve, a greater mean IOP reduction was obtained at nighttime compared to that obtained at daytime: −2.9 (95% CI: −3.5 – −2.1) mmHg (−14.9%) vs −2.3 (95% CI: −2.9 – −1.6) mmHg (−13.6%), suggesting a better performance of the PF-TTFC in IOP control at nighttime (Means and 95% CIs reported in Supplementary Table 2).

Hyperemia and corneal staining were significantly decreased at 3M Visit compared to Baseline Visit (Table 2). Fifty-two percent of patients (20/38) showed a reduction of corneal staining, whereas 4 (10.52%) patients showed a worsening. Hyperemia has improved in 24 (63.3%) of patients and worsened in 2 (5.26%). At Baseline, only 14 (36.8%) patients had none or minimal hyperemia, whereas the number increased to 31 (81.6%) patients at 3M visit. Similarly, the number of patients with no or minimal corneal staining increased from 26 (68.4%) at Baseline to 35 (92.1%) at 3M Visit (Table 2). No statistically significant differences were found in BUT and Schirmer test (Table 2).

At Baseline visit, 11 (28.9%) patients had blepharitis. Of these patients, 4 (10.5%) recovered from blepharitis at 3M visit, after treatment with PF-TTFC. Only 1 (2.6%) new onset moderate blepharitis was reported as non-serious adverse event, probably related to the treatment switch.

IVCM analysis showed that at 3M visit the wing cell average size was significantly decreased at 3M visit, whereas the mean cell density and count were higher, although this increase was not statistically significant (Table 3). In addition, corneal nerve of sub-basal plexus showed no statistically significant difference from Baseline Visit, in either terms count

Table 2 Conjunctival and Corneal Examination

	Baseline Visit	3 Months Visit	P value
Hyperemia Score*	1.8 (0.8)	1.0 (0.6)	<0.001
[n (%)]			
0 – None	1 (2.6%)	3 (15.8%)	<0.001
1 – Minimal	13 (34.2%)	25 (65.8%)	
2 – Mild	17 (43.6%)	7 (18.4%)	
3 – Moderate	7 (18.4%)	0 (0.0%)	
4 – Serious	0 (0.0%)	0 (0.0%)	
5 – Severe	0 (0.0%)	0 (0.0%)	
BUT (s)*	4.0 (2.1)	3.8 (2.5)	0.48
Schirmer test (mm/5 min)*	7.6 (6.4)	8.6 (6.5)	0.46
Corneal Staining			
[n (%)]			
0 – None	8 (21.0%)	16 (42.1%)	0.03
I – Minimal	18 (47.4%)	19 (50.0%)	
II – Mild	9 (23.7%)	3 (7.9%)	
III – Moderate	3 (7.9%)	0 (0.0%)	

Note: *Mean (SD).
Abbreviation: BUT, Breakup time.

Table 3 In vivo Confocal Microscopy Analysis at Baseline vs 3 Months Visit

	Baseline Visit	3 Months Visit	Difference	P value
Corneal nerves				
Mean Count (n)	20.7 [17.2–24.2]	18.2 [14.4–21.7]	−2.5	0.17
Mean Length (µm)	112,883 [71,304–154,461]	132,298 [90,719–173,876]	19,415	0.41
Wing cells				
Mean Count (n)	264 [210–319]	322 [268–375]	57.1	0.12
Mean Density (cells/µm^2)	0.0068 [0.0064–0.0073]	0.0072 [0.0068–0.0077]	0.0004	0.13
Mean Average size (µm^2)	142.7 [138–147]	135.1 [131–140]	−7.57	0.005
Dendritic immune cells				
Mean Count (n)	7.7 [5.41–11.6]	7.6 [5.75–11.7]	0.1	0.9
Mean Density (cells/µm^2)	0.025 [0.018–0.032]	0.021 [0.014–0.027]	0.004	0.3
Mean Length (µm)	11.4 [10.3–12.5]	11.1 [10.3–12.4]	0.3	0.6

or length of the nerves (Table 3) and the mean count, density and length of the dendritic cells at 3M visit were comparable to those found at Baseline Visit (Table 3).

At baseline, the mean DEQ-5 score totaled by study patients was 8.29 which is the value generally scored by patients with suspected Kerato-conjunctivitis sicca.[13] After 3 months from the therapy switch from BAK-Latanoprost to PF-TTFC, the score decreased to 6.13, as result of a reduction in symptoms associated with dry eye in patients ($p = 0.002$).

QoL of the study patients was evaluated both considering the NEI-VFQ25 Composite score, consisting of the mean of 11 subscales explored by the questionnaire (except for "General Health") and each of the 12 single subscales. The estimates of the mean scores of NEI-VFQ25 obtained at the Baseline Visit and at 3M Visit are reported in Supplementary Table 3. No statistically significant differences were found neither regarding the composite score nor other NEI-VFQ25 subscales, after treatment switch to PF-TTFC.

Discussion

The ocular surface disease in glaucoma patients treated with multiple agents and preserved formulations is an emerging problem that can impair ocular surface health, quality of life and ultimately therapy outcomes. In this study, we evaluated the effectiveness PF-TTFC in reducing the mean 24-hour IOP and OSD signs and symptoms in POAG and OHT patients treated with BAK-Latanoprost and with suboptimal IOP control.

According to the 24-hour IOP measurements of this group of patients, switching from BAK-Latanoprost to PF-TTFC resulted in a significant drop in mean 24-hour IOP that was present at all time points, up to 18.5% reduction from baseline at 11 pm. The mean IOP reduction was 14% ranging from 11.3 to 18.5%.

This result is similar to those reported in two previous reports in which patients insufficiently controlled on prostaglandin analogue in monotherapy were switched to TTFC without a washout period.[19–23] The relative mean IOP reduction was 11.2% and 17.6%. Similarly, to our study, the patients recruited in these studies had a relatively lower baseline IOP (16.5 mmHg and 18.2 mmHg vs 17.8 mmHg, respectively). The same authors also showed that greater IOP reduction rates were achieved in patients with higher baseline IOP. This finding may also explain why, in the present study, the IOP reduction was somewhat lower compared to others reported in the literature,[24,25] in which a mean relative reduction of 21.5 and 33% was achieved in patients whose baseline IOP was ≥20 mmHg.

In addition to the individual time points of the 24-h, we also evaluated the mean IOP values obtained at daytime and nighttime, in comparison with the corresponding values at baseline. In this study, both BAK-Latanoprost at baseline and PF-TTFC were administrated in the evening (8 pm). In line with existing evidence in the evening dosing of prostaglandin analogues combined or not with timolol,[26–28] we found that with both therapies the IOP at daytime was significantly lower compared to nighttime. Either BAK-Latanoprost and PF-TTFC provided a better diurnal control than nocturnal, thanks to the peak effectiveness of prostaglandin analogues (with or without timolol) approximately at 12 hours after administration. Nevertheless, compared to the corresponding IOP measurements at baseline, the PF-TTFC efficiently controlled IOP in both day and nighttime, but the effect at nighttime was higher than at daytime, achieving a statistically and clinically significant additional reduction of approximately 3 mmHg during the night. As a consequence, the nocturnal IOP rise was lower with PF-TTFC compared to baseline (+1.9 mmHg vs +2.5 mmHg, respectively), substantiating a better night control. The higher effectiveness at nighttime of the PF-TTCF and in particular at 11 pm may be in part explained by the timolol associated to the tafluprost that has its peak effect at 3–4 hours from administration and may contribute to better IOP control. Moreover, it has been reported that beta-blockers can bind to human iris and ciliary body epithelia, likely providing a consequent slow release of the active agent from these tissues,[29] and this might account for a quite continuous effect on IOP beyond the peak and throughout the 24h. These data are also consistent with the evidence that the addition of beta-blockers in fixed combinations with prostaglandin analogues can provide a meaningful additional reduction in the 24h IOP with either morning or evening administration.[30] Then, our results suggest that PF-TTFC enhances the 24-h IOP reduction and provides uniform control over the 24-h, which, despite some contrasting evidence[31,32] may play a role in the long-term prognosis of glaucoma patients.[33–35]

The cornea and the conjunctiva showed improvements in patients after the therapy switch to PF-TTFC. Hyperemia and corneal staining significantly decreased compared to baseline, resulting in lower perception of the OSD affecting the patients, as expressed by DEQ-5 changes. At the same time, the number of patients showing blepharitis decreased.

Most of the techniques for clinical assessment of OSD are subjective, observer-dependent and variable in consistency of the measurement. The impact of patient experience and perception, however, cannot be underestimated. Improved OSD symptoms and signs, including blepharitis and hyperemia, may result in improved adherence to therapy by patients.[36] NEI-VF 25 questionnaire was also administrated to the patients at baseline and at 3 months of therapy with PF-TTFC. The analysis of the composite score and each single subscale did not show significant improvement in quality of life of the patients. However, our sample size was not calculated to identify differences in quality of life with the NEI-VF 25. Therefore, the study may be underpowered to detect statistically significant differences, and tailored studies are needed to further explore this aspect in more detail. In addition, we postulate that the NEI-VF 25, as well as other questionnaires on vision-related QoL, may not be sensitive enough to highlight significant changes after a short-term therapy switch.

Besides successfully reducing IOP and OSD symptoms, PF-TTFC also showed positive effects on corneal and ocular surface health. Previous studies found that glaucoma patients have lower corneal nerve density and count related to the disease and its treatment.[37,38] Moreover, both reversible and irreversible nerve degeneration were noted in eyes treated with BAK, compared to controls.[39] Furthermore, an increase in dendritic immune cell density is observed with the use of a higher number of active compounds in the therapeutical regimen for glaucoma and in patients treated with preserved compounds rather than preservative-free ones.[40] In the present study, IVCM showed no statistically significant differences following the therapy switch except for the average size of wing cells. According to a recent in vivo confocal microscopy study, patients affected by Dry Eye Disease show irregularly shaped and enlarged wing cells as well as lower cellular density.[41] In our study patients, wing cell average size was significantly decreased after therapy switch from BAK-Latanoprost to PF-TTFC. In addition, the mean cell density and count were higher at 3M Visit, although the increase was not statistically significant. These results may suggest an initial recovery of the homeostasis of corneal epithelium with preservative free therapy. Nevertheless, it may take longer for these parameters to show changes over time.

Some strengths of this study can be pointed out. Enrolled patients showed insufficiently controlled IOP with BAK-Latanoprost at baseline and with signs and symptoms of OSD. Furthermore, the switch to PF-TTFC was made without a washout period between the two therapies. We aimed to replicate conditions reflecting real clinical practice, in which when a monotherapy is insufficient to control the IOP, a second agent is added, possibly in fixed combination, according to the principal guidelines on glaucoma care.[12,42,43] This is also the reason why we chose to compare a monotherapy (BAK-Latanoprost) to a fixed combination (PF-TTFC), instead of comparing two monotherapies (preserved and not preserved). Also, including patients with OSD has the potential advantage to evaluate whether switching therapy has an effect on the population that might actually benefit from it.

A limitation of this study is the relatively short follow-up. A longer evaluation could have provided further evidence on the long-term effectiveness, tolerability and especially on OSD signs and symptoms control. In addition, we did not evaluate the blood pressure of the patients. Beta-blockers have been reported to be associated with the reduction of blood pressure,[44,45] that especially at night may be a potential risk factor for glaucoma progression, probably due to reduced perfusion of the optic nerve head.[46] For this reason, although we did not explore this effect, it should be considered when considering treatment with beta-blockers, especially in patients affected by normal tension glaucoma.

Conclusions

In conclusion, this study showed that in OHT and open-angle glaucoma patients with signs and symptoms of OSD insufficiently controlled on BAK-Latanoprost, the preservative free tafluprost-timolol fixed combination enhanced the 24-h IOP control, in association with a better tolerability profile, improving ocular surface health.

Data Sharing Statement

Any individual deidentified participant data collected and/or analyzed during the current study are available from the corresponding author upon reasonable request from the date of publication of this work.

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Disclosure

FO has served as a consultant and received compensations from AbbVie, Santen SA, Fidia, Visufarma, Thea. LMR has served as a consultant and received compensations from Alcon, AbbVie, iCare, Omikron, Novartis, Santen SA, Fidia, OFFHEALTH, Visufarma, Thea. The authors report no other conflicts of interest in this work.

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