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Twenty-four hour efficacy with preservative free tafluprost compared with latanoprost in patients with primary open angle glaucoma or ocular hypertension

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ABSTRACT

Aim To compare 24 h intraocular pressure (IOP) control obtained with preservative free (PF) tafluprost 0.0015% versus branded preservative containing latanoprost 0.005% administered as first choice monotherapy in patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT).

Methods This prospective, observer-masked, crossover study included consecutive newly diagnosed patients with POAG or OHT, and baseline IOP between 24 and 33 mm Hg. Qualifying patients underwent baseline untreated 24 h IOP monitoring in habitual positions, with Goldmann tonometry at times 10:00, 14:00, 18:00 and 22:00, and Perkins supine tonometry at times 02:00 and 06:00. They were then randomised to either latanoprost or tafluprost, administered in the evening, for 3 months and then switched to the opposite therapy for another 3 months. 24 h monitoring was repeated at the end of each treatment period.

Results 38 patients completed the study. Mean untreated 24 h IOP (24.9 mm Hg) was significantly reduced with both prostaglandins ($p<0.001$). Tafluprost demonstrated similar mean 24 h efficacy compared with latanoprost (17.8 vs 17.7 mm Hg; $p=0.417$). Latanoprost demonstrated significantly better 24 h trough IOP (15.9 vs 16.3 mm Hg; $p=0.041$) whereas tafluprost provided significantly lower 24 h IOP fluctuation (3.2 vs 3.8 mm Hg; $p=0.008$). No significant difference existed between the two prostaglandins for any adverse event.

Conclusions PF tafluprost achieved similar 24 h IOP reduction to branded latanoprost. The current study highlights the importance of complete assessment of efficacy over 24 h.

Clinical trials registration NCT01162603.

INTRODUCTION

Prostaglandin analogues have become a popular firstline therapeutic option for the decrease in intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension (OHT) due to their superior 24 h potency, convenient dosing and favourable systemic safety profile. Until recently, all available prostaglandin analogues were formulated as preservative containing solutions. Preservatives used in ophthalmic solutions, and in particular benzalkonium chloride (BAK), have been associated with ocular tissue toxicity and decreased long term tolerability, thus potentially limiting adherence and undermining the success of chronic medical therapy.[1–5] Long term tolerability has emerged as a key issue for the successful management of glaucoma patients. Furthermore, there is growing recognition that preservatives are associated with ocular surface disease, which negatively impacts on quality of life in glaucoma patients.[6]

Tafluprost 0.0015% is a relatively new prostaglandin analogue that first became commercially available as a BAK preserved formulation. The first studies indicated that the IOP lowering effect of preserved tafluprost is comparable, or slightly inferior, to that of latanoprost[7 8] and travoprost.[9] More recently, a preservative free (PF) formulation of tafluprost has been made available in several countries worldwide.[10–17] The comparative efficacy of PF tafluprost versus other prostaglandins needs to be further elucidated in controlled prospective studies.

To date, the 24 h efficacy of PF tafluprost has not been determined. In order to select the optimal initial monotherapy, it is important to compare the efficacy of all available prostaglandin analogues over 24 h. Therefore, the present investigation evaluated the 24 h IOP efficacy of PF tafluprost 0.0015% versus BAK preserved branded latanoprost 0.005% when both were administered as first choice therapy in patients with primary open angle glaucoma (POAG) or OHT.

MATERIALS AND METHODS

The research protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review boards of the participating centres. Written informed consent was obtained from all participants prior to enrolment. The trial was registered at clinicaltrials.gov (NCT01162603).

Consecutive adults with newly diagnosed POAG or OHT were recruited at two participating centres. Eligible subjects had to exhibit untreated sitting morning IOP, evaluated with Goldmann tonometry, of 24–33 mm Hg in the study eye on two separate baseline IOP measurements performed at time 10:00 (±1 h). Additional eligibility criteria were central corneal thickness between 500 and 600 µm and age 39–85 years. In each case, the diagnosis of POAG or OHT was made by one of two glaucoma specialists (AGPK or LQ) based on the European

Glaucoma Society criteria following a comprehensive clinical examination.

Exclusion criteria for ophthalmic conditions were corneal or other anatomical abnormalities preventing reliable applanation tonometry, severe dry eye, use of contact lenses, intolerance or contraindication to latanoprost, tafluprost or BAK, history of poor medication adherence, laser treatment or ocular surgery of any type in the study eye, best corrected visual acuity less than Snellen 0.1, mean deviation worse than −12 dB on Humphrey 24–2 SITA standard perimetry, cup to disc ratio >0.8, or the possibility of optic nerve damage and visual function deterioration due to study procedures according to the investigator's judgment. Exclusion criteria for systemic conditions were pregnancy or lactation, unwillingness to avoid pregnancy and use of corticosteroids within the 2 months before enrolment.

Procedures

The trial was designed as a prospective, randomised, observer masked, active controlled, crossover study. First, eligible participants were admitted at the participating academic centres and underwent baseline untreated 24 h IOP monitoring in habitual positions, with Goldmann sitting tonometry, at times 10:00, 14:00, 18:00 and 22:00, and Perkins supine tonometry at times 02:00 and 06:00 (±1 h). In each centre, the same calibrated Goldmann and Perkins tonometers were used for all measurements. In all cases, the investigator who performed the IOP measurements was blinded to the treatment regimen. Following the untreated 24 h IOP curve, participants were randomised to either 3 months of chronic therapy with preserved latanoprost 0.005% solution (Xalatan; Pfizer) dosed in the evening (20:00), or to 3 months of therapy with PF tafluprost 0.0015% solution (Saflutan; MSD) dosed also in the evening (20:00). Both eyes were treated. Instructions regarding correct eyedrop instillation and adherence were also provided. At the end of this initial 3 month treatment period, all participants underwent a treated 24 h IOP assessment, as previously described. Patients were then crossed over to the opposite prostaglandin therapy for another 3 months and instructions regarding correct eyedrop instillation and adherence were repeated. At the end of this final therapy period, participants underwent a third 24 h IOP curve with identical methodology. A comprehensive clinical examination was performed at all visits. Additionally, patient reported complains and symptoms, as well as investigator noted adverse events, were recorded at the end of each treatment period.

Statistics

The primary efficacy endpoint for this study was mean 24 h IOP. Individual time points, peak, trough and fluctuations in 24 h IOP were evaluated as secondary endpoints. The study had 80% power to identify a 1.25 mm Hg difference between individual time points and between the mean 24-h IOP, assuming an SD of 2.8 mm Hg between the two prostaglandin monotherapies. One randomly selected eye per participant was analysed. A mixed model was used for the crossover repeated measures design to adjust for period and carryover effects.[18] Additionally, the model was adjusted for the centre effect. A 95% CI was constructed for the adjusted difference in means. An intention to treat approach was adopted, and subjects were analysed according to their randomised group.

To correct for multiple comparisons at individual time points, a Bonferroni adjustment was used. Thus Bonferroni adjusted p values are reported for individual time point comparisons. All other reported p values are two tailed, with $p<0.05$ considered significant. Mean 24 h IOP fluctuation was defined as the average of the difference between the highest IOP reading minus the lowest IOP reading within the 24 h curve for each patient. Adverse events were evaluated using a McNemar test. All analyses were conducted using IBM-SPSS 20.0.

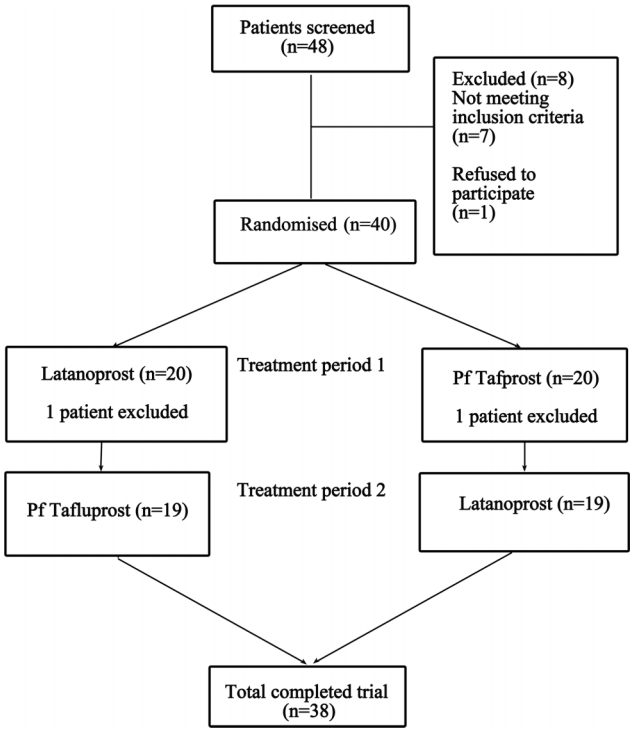

Figure 1 Flowchart of the study participants.

RESULTS

Patients

Thirty-eight of 40 enrolled participants completed the study. Their flowchart and demographics are presented in figure 1 and table 1. Two study patients (one in each therapy group) were lost to follow-up.

Intraocular pressure

Compared with untreated baseline readings, mean 24 h, peak, trough, fluctuation and IOP at individual time points were all significantly reduced with both prostaglandin monotherapies ($p<0.001$ for all comparisons) (table 2). When the two prostaglandins were directly compared, PF tafluprost demonstrated similar mean 24 h efficacy compared with preserved latanoprost (17.8±2.2 vs 17.7±2.1 mm Hg; $p=0.417$). Furthermore, there

Table 1 Participant demographics

Characteristic	
Sex (M/F)	18/20
Age (years)	66.7 (9.1)
CCT (μm)	551 (24.4)
Snellen BCVA	0.8 (0.2)
C/D	0.6 (0.1)
MD (dB)	5.41 (3.1)

Values are mean (SD) or number.
BCVA, best corrected visual acuity; CCT, central corneal thickness; C/D, cup/disc ratio; MD, mean deviation.

Table 2 Intraocular pressure results at baseline and after treatment with the study medications

IOP measurements (time)	Baseline (mean (95% CI))	Latanoprost (mean (95% CI))*	PF tafluprost (mean (95% CI))*	Adjusted difference (mean (95% CI))*	p Value
06:00	25.1 (24.2 to 26.0)	17.5 (16.7 to 18.3)	17.5 (16.8 to 18.4)	0.00 (−0.44 to 0.44)	1.000†
10:00	26.9 (26.1 to 27.7)	17.9 (17.0 to 18.8)	18.4 (17.5 to 19.3)	−0.50 (−1.03 to 0.03)	0.372†
14:00	24.1 (23.2 to 25.0)	17.3 (16.5 to 18.2)	17.8 (17.0 to 18.6)	−0.47 (−1.05 to 0.10)	0.624†
18:00	23.8 (23.0 to 24.6)	17.3 (16.4 to 18.1)	17.7 (16.8 to 18.5)	−0.39 (−0.88 to 0.09)	0.648†
22:00	24.9 (23.8 to 26.0)	17.8 (16.9 to 18.8)	17.6 (16.6 to 18.5)	0.24 (−0.20 to 0.67)	1.000†
02:00	24.4 (23.6 to 25.2)	18.0 (17.2 to 18.9)	17.6 (16.8 to 18.4)	0.45 (−0.07 to 0.96)	0.516†
Mean 24 h	24.9 (24.2 to 25.5)	17.7 (16.9 to 18.4)	17.8 (17.0 to 18.5)	−0.11 (−0.39 to 0.17)	0.416
Peak 24 h	27.7 (26.8 to 28.6)	19.7 (18.8 to 20.5)	19.5 (18.6 to 20.3)	0.24 (−0.18 to 0.66)	0.277
Trough 24 h IOP	18.3 (17.8 to 18.8)	15.9 (15.2 to 16.6)	16.3 (15.6 to 17.0)	−0.39 (−0.78 to −0.01)	0.041
24 h fluctuation	3.7 (3.4 to 4.0)	3.8 (3.2 to 4.3)	3.2 (2.6 to 3.7)	0.63 (0.18 to 1.08)	0.008

Depicted p values refer to comparison between latanoprost and PF tafluprost. All comparisons between baseline and latanoprost or preservative free tafluprost were statistically significant ($p<0.001$).
*Adjusted for period, carryover effect and centre.
†Bonferroni adjusted p values.
IOP, intraocular pressure; PF, preservative free.

were no statistically significant differences for individual time points (table 2, figure 2).

With regard to other 24 h IOP characteristics, PF tafluprost demonstrated significantly lower 24 h IOP fluctuation (3.2±1.7 vs 3.8±1.8 mm Hg; p=0.008). In contrast, latanoprost provided significantly lower 24 h trough IOP (15.9±2.1 vs 16.3 ±2.2 mm Hg; p=0.041). There was no significant difference in 24 h peak IOP between the two prostaglandins (19.7 vs 19.5 mm Hg, respectively; p=0.277) (table 2).

Adverse events

No serious adverse events and no adverse event related withdrawal occurred during the study. In addition, there was no significant difference between the two agents for any adverse event (table 3). Overall, the number of adverse events with latanoprost and PF tafluprost treatment were 22 and 14, respectively. The most frequently encountered adverse event was ocular hyperaemia (n=6 during latanoprost treatment period; n=5 during PF tafluprost treatment period).

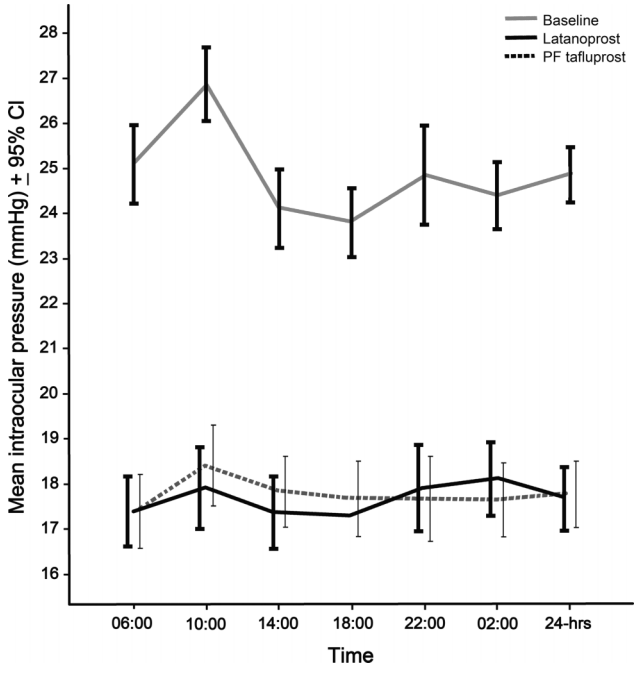

Figure 2 Intraocular pressure (mean±95% CI) at each individual time point and for the 24 h pressure at baseline (gray solid line), in the latanoprost (solid black line) and preservative free (Pf) tafluprost (black dotted line) treatment groups.

DISCUSSION

The present study is the first to evaluate the 24 h efficacy of PF tafluprost compared with branded preserved latanoprost as a first choice monotherapy in newly diagnosed patients with POAG or OHT. The results showed identical mean IOP lowering over 24 h (mean 24 h IOP difference was only 0.1 mm Hg). Greater 24 h trough IOP reduction was observed during latanoprost therapy while significantly lower 24 h IOP fluctuation was documented with PF tafluprost.

Tafluprost, a fluorinated analogue of prostaglandin F_{2a}, is a potent and selective agonist of the human prostanoid FP receptor with a reported 12 fold greater affinity for the FP receptor than latanoprost.[19] It was first introduced in Japan in 2008 as a BAK containing multidose formulation, and in Germany in 2008 with approval for both a preserved and a PF tafluprost formulation.[20 21] Currently, however, throughout the rest of the world, only the PF formulation is marketed.[20 21] Initial reports in healthy eyes indicated that preserved tafluprost was at least as well tolerated and safe as preserved latanoprost when used over short periods.[22–25] Furthermore, it was demonstrated that the efficacy of preserved tafluprost was comparable with that of preserved latanoprost in healthy volunteers.[22–26]

Due to its short marketing history, there are limited long term efficacy data for preservative containing tafluprost in patients with glaucoma or OHT. Two studies have reported that preserved tafluprost attained a mean diurnal IOP reduction of 28.6% and 29.1%, respectively, from untreated baseline.[8 9] A third short term phase II study[7] reported that the mean IOP change from baseline of preserved tafluprost was similar to that of branded latanoprost after 42 days (−9.7 mm Hg for tafluprost and −8.8 mm Hg for latanoprost). In a 24 month, parallel, double blind, multicenter study performed by Uusitalo *et al*,[8] tafluprost lowered daytime IOP by 6–8 mm Hg (27–31%) compared with 7–9 mm Hg (29–35%) with branded latanoprost. In this study, after 24 months of therapy, the mean decrease in IOP from baseline was reported to be somewhat superior with latanoprost (−7.7 mm Hg, 32.2%) than preserved tafluprost

Table 3 Adverse events of the study medications

Adverse event	Latanoprost	PF tafluprost		n (%)	p Value
		Yes	No	Total	
Ocular hyperaemia	Yes	2	4	6 (15.8)	1.000
	No	3	29	32 (84.2)	
n (%)	Total	5 (13.2)	33 (87.8)	38 (100)	
Stinging	Yes	1	3	4 (10.5)	1.000
	No	3	31	34 (89.5)	
n (%)	Total	4 (10.5)	34 (89.5)	38 (100)	
Foreign body sensation	Yes	0	2	2 (5.3)	1.000
	No	2	34	36 (94.7)	
n (%)	Total	2 (5.3)	36 (94.7)	38 (100)	
Blurring of vision	Yes	1	3	4 (10.5)	0.250
	No	0	34	34 (89.5)	
n (%)	Total	1 (2.6)	37 (97.4)	38 (100)	
Watering	Yes	1	1	2 (5.3)	1.000
	No	0	36	36 (94.7)	
n (%)	Total	1 (2.6)	37 (97.4)	38 (100)	
Itchiness	Yes	0	2	2 (5.3)	0.500
	No	0	36	36 (94.7)	
n (%)	Total	0 (0)	38 (100)	38 (100)	
Burning	Yes	0	2	2 (5.3)	0.500
	No	0	36	36 (94.7)	
n (%)	Total	0 (0)	38 (100)	38 (100)	
Ocular ache	Yes	0	0	0 (0)	1.000
	No	1	37	38 (100)	
n (%)	Total	1 (2.6)	37 (97.4)	38 (100)	

PF, preservative free.

(−7.1 mm Hg, 29.1%).[8] This study demonstrated that the non-inferiority criterion for tafluprost was reached with ANOVA and almost reached with ANCOVA for all daytime IOP measurements.

There is convincing evidence suggesting that PF tafluprost exhibits comparable efficacy to preserved tafluprost. First, a pharmacokinetic study[27] did not detect a difference in systemic bioavailability between the two formulations after 8 days. Second, Hamacher *et al*[10] evaluated the IOP lowering equivalency between the two formulations and observed an overall efficacy difference of only 0.01 mm Hg (95% CI −0.46 to 0.49; p=0.96) at 4 weeks.

Several open label non-interventional studies have examined the efficacy and tolerability of PF tafluprost in naïve[16] or previously treated patients with open angle glaucoma or OHT, who were either poorly controlled or had tolerability issues with other medications.[12–15 28] Overall, these investigations have reported a mean diurnal IOP reduction of 22.9–32.1% from untreated baseline.[13 16 28] Although these studies do not provide controlled observations, they indicate that PF tafluprost has almost comparable efficacy to latanoprost and will likely benefit patients facing tolerability problems with other medications. Similar IOP results were reported in a prospective investigator masked study.[29] In a more recent regulatory double masked comparative trial, Chabi *et al*[11] demonstrated in patients with open angle glaucoma or OHT that PF tafluprost was generally well tolerated and was not inferior to PF timolol administered twice daily.

The current trial investigated for the first time the 24 h IOP efficacy provided by a PF tafluprost versus branded latanoprost, a well established initial therapy of choice. Both agents provided clinically meaningful 24 h IOP reduction from baseline (28.5% for PF tafluprost and 29.3% for latanoprost). These results are comparable with the reported 24 h efficacy of the three previously available prostaglandin analogues, as reported in a meta-analysis by Stewart *et al* (24–29%).[30] A 24 h IOP curve may better delineate IOP characteristics and facilitate glaucoma management. Thus our study provides evidence to optimise selection between available prostaglandin analogues as initial therapy.

This efficacy profile would not have been detected without a complete 24 h IOP evaluation. Thus the present study highlights the value of a complete efficacy assessment over 24 h in determining the true IOP lowering characteristics of a novel antiglaucoma medication. In a previous 24 h IOP study in 30 healthy Japanese subjects, Mochizuki *et al* compared the efficacy of tafluprost and branded latanoprost.[25] Apart from the differences in study populations and despite several methodological differences (timing of drug administration, duration of therapy and different time of IOP measurements), it is interesting to note the similarities in findings between the two 24 h studies. The Mochizuki study[25] also observed a mean 24 h difference of 0.1 mm Hg and the two prostaglandins exhibited similar tendencies to preferentially lower IOP during the day (latanoprost) and night (tafluprost). In contrast with the present study, however, these IOP lowering differences reached statistical significance in the Japanese study.

In the present study, PF tafluprost achieved significantly less 24 h IOP fluctuation than branded latanoprost. Twenty-four hour IOP fluctuation and 24 h peak IOP have emerged in some 24 h studies[31–33] as potential risk factors for glaucoma progression. This has brought attention to the 24 h IOP lowering

profiles with topical medications.[34 35] Based on the notion that increased circadian IOP fluctuation may be harmful for some glaucoma patients, it may be clinically desirable to opt for favourable 24 h IOP characteristics, such as low 24 h IOP fluctuation and low 24 h peak IOP. However, the potential long term clinical benefit of improved 24 h IOP control requires further elucidation.

The current study was a short term monotherapy study and it did not have sufficient power to determine long term safety or tolerability. Both medications were well tolerated without serious adverse events or adverse event related study withdrawals. There was no significant difference in the incidence of individual adverse events. Nevertheless, the adverse events observed in our trial may not accurately portray the true long term tolerability profile of these agents.

Glaucoma requires lifelong treatment and thus long term tolerability is an issue of clinical importance. Cumulative evidence shows that long term topical treatment with antiglaucoma medications leads to the manifestation, or exacerbation, of symptoms and signs of ocular surface disease.[3 36] As a consequence, patient's quality of life can decline and adherence may be adversely affected.[37–42] There is convincing evidence that long term exposure to preservatives, and especially BAK, can cause histopathological changes in ocular tissues that can adversely affect the success of subsequent glaucoma surgery.[4 5] PF medications have become increasingly popular in glaucoma due to their reduced potential for ocular toxicity with presumed enhanced tolerability and improved adherence.[1 38 43 44] The observation of similar drug efficacy versus available preservative containing treatment options may encourage greater use of PF medications. On the other hand, more evidence is needed to confirm the long term potential benefits accrued with the use of PF medications, such as improved medication adherence leading to better long term visual outcomes. By demonstrating comparable 24 h efficacy to branded latanoprost, PF tafluprost can be considered as a reasonable firstline choice in glaucoma therapy.

Contributors The study was designed by AGPK and LQ. Data collection was performed by IR, A-BH, TG, ICV and EP. Data analysis and interpretation was performed by IF, A-BH, AGPK and LQ. The manuscript was drafted by AGPK, AK and IR. Critical revision of the manuscript was done by AGPK, LQ and JCT. All authors read and approved the final version of the article.

Competing interests AGPK is a consultant for Alcon, Allergan, MSD and Nicox. AGPK has received honoraria or travel reimbursement from Alcon, Allergan and Pfizer. LQ has received honoraria or travel reimbursement from Alcon, Allergan, MSD, Thea Farmila, and Bausch and Lomb. AK has received travel reimbursement from Alcon and MSD. IR has received travel reimbursement from Alcon and MSD.

Ethics approval The study was approved by the institutional review board of the Medical School of Aristotle University, Thessaloniki, Greece, and the institutional review board of the Clinica Oculistica, University of Brescia, Brescia, Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

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