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A Comparative, Placebo-Controlled Study of Prostanoid Fluoroprostaglandin-Receptor Agonists Tafluprost and Latanoprost in Healthy Males

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ABSTRACT

Objective: **The aim of this study was to determine the safety, tolerability, and pharmacodynamics of a novel prostanoid fluoroprostaglandin (FP)-receptor agonist, tafluprost (AFP-168), in healthy males.**

Methods: **This was a phase I study in healthy males 18–45 years of age (N = 49). Participants were randomized to receive 1 of 4 eye drops: tafluprost 0.0025% or 0.005%, latanoprost 0.005%, or a placebo, administered once-daily for 7 days, with 1 drop per eye. Safety and tolerability assessments and intraocular pressure (IOP) measurements were performed at defined intervals.**

Results: **Tafluprost was generally well tolerated. No serious adverse events were reported and no participants withdrew owing to an adverse event. IOP decreased over time, compared with baseline, in all 4 treatment groups. Treatment with tafluprost 0.005% resulted in a significantly greater reduction in IOP, compared with either latanoprost 0.005% or a placebo, at various time points during treatment. Ocular hyperemia and photophobia were more common with tafluprost 0.0025% or 0.005%, compared with latanoprost 0.005%.**

Conclusions: **Tafluprost eye drops 0.0025% and 0.005% were generally well tolerated and safe. Tafluprost 0.005% reduced IOP more than placebo or latanoprost 0.005%. Therefore, tafluprost looks promising for further investigation.**

INTRODUCTION

In patients with primary open-angle glaucoma, severity of increased intraocular pressure (IOP) is linked to the death of ganglion cells and optic nerve fibers and, consequently, visual impairment.[1] IOP may be effectively reduced with prostaglandin derivatives that stimulate prostanoid receptors. Latanoprost, a selective prostanoid fluoroprostaglandin (FP)-receptor agonist, has effectively reduced IOP in both short- and long-term clinical trials.[2,3] Long-term use of latanoprost and other prostaglandin analogs, however, is associated with increased iris and skin pigment, possibly as a result of increased melanogenesis.[4] The incidence of iris pigmentation increases with prolonged therapy, with enhanced pigmentation being noted in 56% of patients who use latanoprost for 1 year.[5] A retrospective study identified iris pigmentation in 43% of latanoprost users, with

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chemosis in 3% and lid margin pigmentation in 2%.[6]

In an effort to reduce adverse events, new prostanoid FP-receptor agonists have been developed with fluorine(s) in the 15-position. Studies in cultured melanoma cells have shown a reduced melanin content with some of these newer compounds.[7] Tafluprost (AFP-168) is a new, recently synthesized, selective prostanoid FP-receptor agonist.[8] Preclinical studies of tafluprost showed a superior FP-receptor affinity and agonism, compared with latanoprost.[7,9] In addition, tafluprost showed a greater potency in lowering IOP, compared with latanoprost, in both ocular normotensive and hypertensive monkeys.[9]

This study was designed to determine the safety, tolerability, and pharmacodynamics of tafluprost in healthy volunteers.

METHODS

This was a phase I, active-comparator, placebo-controlled study. Before the start of this study, the protocol was approved by a local independent ethics committee. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki. Written, informed consent was obtained from all participants prior to their inclusion in the study.

Participants

Healthy males with no significant eye disease were eligible for enrollment. Good general health was determined by the results of a physical examination that was performed within 15 days of enrollment, as well as an electrocardiogram (ECG) and laboratory tests that were performed within 30 days of enrollment. The study enrolled participants 18–45 years of age. Participants were not allowed to wear contact lenses for 1 week before enrollment and during the study. Furthermore, participants were not allowed to smoke for 6 h before enrollment and during the study. Participants were excluded if they had used any systemic or ophthalmic medications 1 week prior to enrollment or had a history of drug or alcohol abuse.

Study design

The participants were randomized to receive 1 of 4 possible eye drops: tafluprost 0.0025% or 0.005% (Santen Oy; Tampere, Finland), latanoprost 0.005% (Pharmacia Corporation; Stockholm, Sweden), or a placebo. The vehicle for tafluprost was used as the placebo. The study was masked for the two concentrations of tafluprost and placebo. Latanoprost was administered in its original bottle. All participants received a once-daily administration of the eye drops for 7 days. For each treatment, a single drop was instilled into each eye by a nurse. Although latanoprost should, according to the label, be used as a nighttime therapy, the instillation of all drops in this study was performed in the morning to allow for daytime post-treatment observation.

All safety and tolerability measures were obtained at pretreatment baseline and at specified times after treatment. Adverse events were recorded 1, 2, 4, 8, 12, and 24 h after treatment on days 1 and 7. Adverse events were also recorded 12 and 24 h after treatment on days 2–6. Vital signs were recorded 2 and 12 h after treatment on days 1 and 7, as well as 24 h after treatment on day 7. Laboratory tests—including a blood work-up for hematology and chemistry, and a urine dipstick and microscopy—were performed 24 h after treatment on day 7. An ECG was obtained 5 min after treatment on days 2 and 6, and 24 h after treatment on day 7.

Ocular safety was evaluated by using a variety of measures. Visual acuity was evaluated 4 and 24 h after treatment on days 1 and 7, as well as 12 h after treatment on days 2–6. Aqueous flare was evaluated using a laser flare cell meter 1, 2, 4, 8, 12, and 24 h after treatment on days 1 and 7. A fundoscopic examination was performed 12 h after treatment on day 3 and 24 h after treatment on day 7. Iris and optic-disk photographs were taken 24 h after treatment on day 7. A biomicroscopy was performed 1, 2, 4, 8, 12, and 24 h after treatment on days 1 and 7, and 12 h after treatment on days 2–6.

Pharmacodynamic response was assessed by measuring pre- and post-treatment IOP. Post-treatment recordings were obtained 1, 2, 4, 8, 12, and 24 h after treatment on days 1 and 7. IOP was also recorded 12 h after treatment on days 2–6.

Data analysis

Given that this was an exploratory study, no formal calculation for sample size was performed. Selected sample sizes were based on typical numbers that were used in phase I glaucoma studies for similar products.

Table 1. Demographics of the Participants

	Tafluprost 0.0025%	*Tafluprost 0.005%*	*Latanoprost 0.005%*	*Placebo*
Total, n	13	11	12	12
Mean age (range), years	27.2 (18–37)	25.7 (18–35)	27.9 (22–45)	27.8 (20–44)
Ethnic group, n				
White	12	8	9	11
Black	0	1	1	1
Asian	0	2	2	0
Other	1	0	0	0

Quantitative variables were summarized by using descriptive statistics. Changes in vital signs and laboratory measures were evaluated by using paired *t* tests. A Dunnett's test was applied when performing pair-wise comparisons of the two tafluprost doses and placebo. A comparison of changes in IOP for tafluprost and placebo versus latanoprost was performed by using individual *t* tests for each time point. For all tests, a *P*-value of 0.05 or less was considered to be significant.

RESULTS

Participants

A total of 49 participants were enrolled in the study. Participants were randomized to receive tafluprost 0.0025% (N = 13), tafluprost 0.005% (N = 12), latanoprost (N = 12), and placebo (N = 12). Treatment was completed by 48 (98.0%) of the participants. One (1) participant who was randomized to tafluprost 0.005% withdrew consent prior to the start of treatment.

Demographic data for participants receiving any treatment are shown in Table 1. There were no baseline ocular symptoms in any of the participants.

Safety and tolerability

There were no notable differences between the treatment groups in terms of systemic safety (Table 2). The number of subjects who reported at least one adverse event was comparable between all treatment groups: 4 in the tafluprost 0.0025% group, 3 in the tafluprost 0.005% group, 4 in the latanoprost 0.005% group, and 4 in the placebo group. Very few systemic adverse events were reported, and all of these were considered to be mild to moderate in severity. Overall, 6 subjects reported a headache (Table 2). Three (3) of these events were considered to be related to the study drug (1 subject each in the tafluprost 0.0025%, the latanoprost 0.005%, and the placebo

Table 2. Systemic Adverse Events

	Tafluprost 0.0025%	*Tafluprost 0.005%*	*Latanoprost 0.005%*	*Placebo*
Palpitations	1 (8)	0	0	0
Dry throat	0	0	1 (8)	0
Fatigue	1 (8)	0	0	0
Nasopharyngitis	0	1 (9)	0	0
Injury NOS	0	2 (18)	0	0
Abnormal liver function	0	0	0	1 (8)
Dizziness	1 (8)	1 (9)	0	0
Headache	2 (15)	1 (9)	2 (17)	1 (8)
Syncope	0	1 (9)	0	0
Epistaxis	0	1 (9)	0	0
Sneezing	0	0	1 (8)	0

Note. Data are n (%).
NOS, not otherwise specified.

Table 3. Ocular Adverse Events

	Tafluprost 0.0025%	*Tafluprost 0.005%*	*Latanoprost 0.005%*	*Placebo*
Foreign-body sensation	1 (8)	0	0	0
Chemosis	2 (15)	0	0	0
Dry eye NEC	3 (23)	0	0	0
Eye pain	2 (15)	4 (36)	3 (25)	0
Eye irritation	1 (8)	3 (27)	1 (8)	0
Keratitis NEC	0	1 (9)	1 (8)	0
Lacrimation	0	1 (9)	0	0
Ocular hyperemia[a]	7 (54)	6 (55)	2 (17)	0
Optic-disk disorders	1 (8)	0	0	0
Photophobia	4 (31)	4 (36)	0	0
Tired eyes	1 (8)	0	0	1 (8)
Blurred vision	0	0	3 (25)	0

Note. Data are n (%).
NEC, not elsewhere classified.
[a]Includes "bloodshot eye."

group). No participants discontinued the study as a result of systemic adverse events.

There were no clinically significant changes in laboratory parameters and vital signs throughout the course of the study. All participants had normal ECGs with sinus rhythm at every ECG assessment.

Ocular adverse events were reported by 9 subjects in the tafluprost 0.0025% group, 10 subjects in the tafluprost 0.005% group, 6 subjects in the latanoprost 0.005% group, and 1 subject in the placebo group (Table 3). All ocular adverse events were nonserious, and of mild or moderate severity. Nearly all were considered to be related to active therapy or placebo. No participant withdrew as a result of ocular adverse events. Ocular hyperemia was the most common adverse events and was reported both with tafluprost and latanoprost, but was more common with either concentration of tafluprost (tafluprost 0.0025%,

Table 4. Conjunctival Redness

		Conjunctival redness				
	Time point	*None*	*Mild*	*Moderate*	*Severe*	*Very severe*
Tafluprost 0.0025%	Day 1 + 8 h	1 (8)	8 (62%)	4 (31%)	0	0
	Day 1 + 12 h	3 (23)	6 (46%)	4 (31)	0	0
	Day 4 + 12 h	7 (54)	6 (46%)	0	0	0
	Day 7 + 8 h	7 (54)	6 (46%)	0	0	0
	Day 7 + 12 h	8 (62)	5 (38%)	0	0	0
Tafluprost 0.005%	Day 1 + 8 h	1 (9)	7 (64%)	3 (27%)	0	0
	Day 1 + 12 h	2 (18)	7 (64%)	2 (18%)	0	0
	Day 4 + 12 h	4 (36)	5 (50%)	0	1 (10%)	0
	Day 7 + 8 h	1 (9)	8 (73%)	2 (18%)	0	0
	Day 7 + 12 h	4 (36)	6 (55%)	1 (9%)	0	0
Latanoprost 0.005%	Day 1 + 8 h	5 (42)	6 (50%)	1 (8%)	0	0
	Day 1 + 12 h	6 (50)	6 (50%)	0	0	0
	Day 4 + 12 h	7 (58)	5 (42%)	0	0	0
	Day 7 + 8 h	6 (50)	5 (42%)	1 (8%)	0	0
	Day 7 + 12 h	8 (67)	4 (33%)	0	0	0
Placebo	Day 1 + 8 h	7 (58)	5 (42%)	0	0	0
	Day 1 + 12 h	10 (83)	2 (17%)	0	0	0
	Day 4 + 12 h	12 (100)	0	0	0	0
	Day 7 + 8 h	11 (92)	1 (8%)	0	0	0
	Day 7 + 12 h	11 (92)	1 (8%)	0	0	0

Note. Data are n (%).
h, hours.

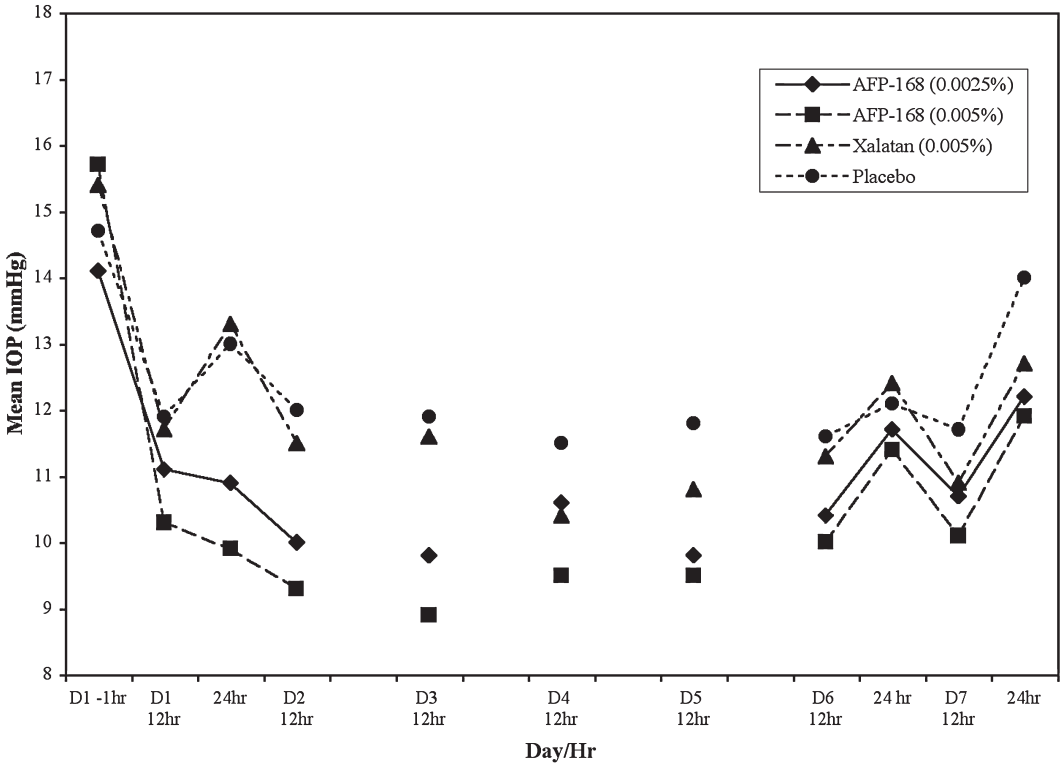

FIG. 1. Mean intraocular pressure (IOP) over time.

n = 7; tafluprost 0.005%, n = 6; and latanoprost 0.005%, n = 2). There were more reports of photophobia in the tafluprost groups (tafluprost 0.0025% and tafluprost 0.005%; n = 4 for both) than in the latanoprost group (n = 0), but more reports of blurred vision in the latter (n = 3), compared with both tafluprost groups (n = 0).

Visual acuity testing showed no notable differences between the treatment groups. All treatments similarly showed a change of <2 lines in

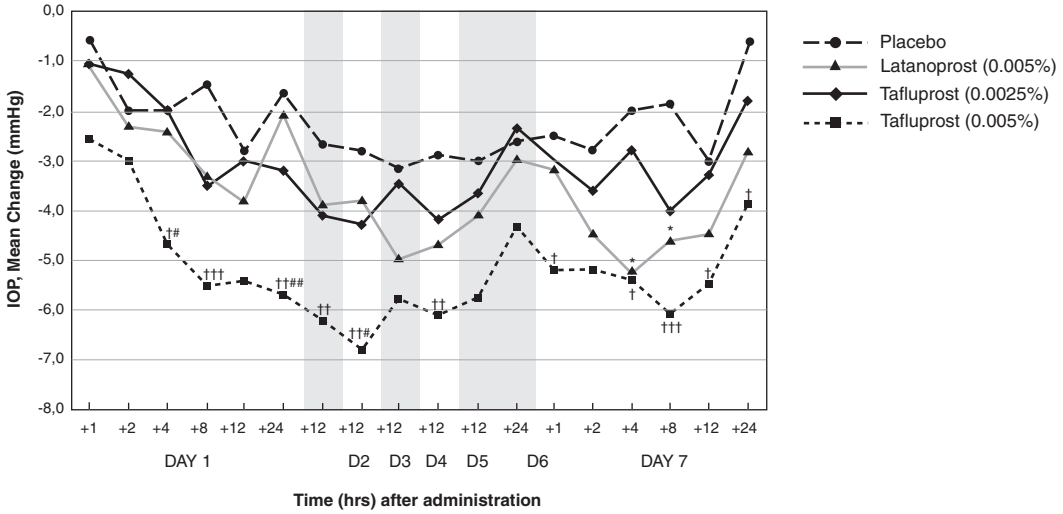

FIG. 2. Change in intraocular pressure (IOP) in healthy males by treatment group. There were no significant differences in mean IOP reduction from baseline between tafluprost 0.0025% and placebo, or latanoprost 0.005%, at any time point. $^{\dagger}p < 0.05$; $^{\dagger\dagger}P < 0.01$; $^{\dagger\dagger\dagger}P < 0.001$, tafluprost 0.005% versus placebo. $^{\#}P < 0.05$; $^{\#\#}P < 0.01$, tafluprost 0.005% versus latanoprost 0.005%. $^{*}P < 0.05$, latanoprost 0.005% versus placebo.

distant visual acuity in the majority of the participants. In all groups, mean aqueous flare decreased slightly over time at the majority of time points, compared with baseline. A fundoscopic examination and photographs of the irises and disks showed no changes in any participant.

A biomicroscopy identified mild post-treatment eyelid redness in 2 (15%) of the participants who were receiving tafluprost 0.0025% and in 1 (9%) who was receiving tafluprost 0.005%. Conjunctival redness was the most frequent ocular event. There were more reports of ocular hyperemia in both tafluprost groups than in the latanoprost group. Most cases were mild or moderate, with 1 report of severe redness (Table 4).

Mild chemosis was reported in 1 participant who was receiving tafluprost 0.0025%, 2 receiving tafluprost 0.005%, 1 receiving latanoprost, and 1 receiving placebo. Two (2) participants who were receiving tafluprost 0.0025% experienced moderate chemosis.

The lower palpebral conjuctiva were graded as having no or mild follicles throughout treatment for all participants. There were no findings in the lens or vitreous for any participant. Abnormal corneal staining was seen in 2 participants who were treated with tafluprost 0.0025%, 1 treated with tafluprost 0.005%, and 2 treated with latanoprost.

Pharmacodynamics

The mean IOP over time is presented in Figure 1. Significant decreases in IOP versus baseline were seen in participants at most or all time points for all treatment groups (Fig. 2). The greatest mean change observed was −4.3 mmHg (28.7%) with tafluprost 0.0025%, −6.8 mmHg (42.7%) with tafluprost 0.005%, −5.3 mmHg (32.3%) with latanoprost, and −3.1 mmHg (20.1%) with placebo. There was a greater reduction in IOP at most points with tafluprost 0.005%, compared with placebo, and for several time points with tafluprost 0.005%, compared with latanoprost.

DISCUSSION

This controlled phase I study tested the safety and change in IOP with tafluprost in healthy adult males. Systemic safety and tolerability were similar with tafluprost, latanoprost, and placebo. All adverse events were mild to moderate and did not result in a treatment discontinuation. Headache was the only systemic adverse event that was considered to be related to the study drug, but was equally distributed among the study groups, including placebo, and, therefore, no conclusion could be drawn. There were no serious ocular adverse events or major findings on biomicroscopy with tafluprost. There were more reports of ocular hyperemia and photophobia with tafluprost, compared with latanoprost, but more reports of blurred vision with the latter, compared with the tafluprost groups. However, the small number of subjects in each treatment group (n = 11–13) required caution to be taken when interpretating the results, and further studies are warranted.

In this study, tafluprost seemed to cause more ocular hyperemia and photophobia than latanoprost. As these adverse events may be dose dependent, further studies are needed to establish the tafluprost dose that would offer the most optimal risk-benefit profile.

IOP decreased with all treatments, but IOP reductions with tafluprost 0.005% were superior to those with placebo and latanoprost 0.005%.

This study was limited by factors inherent to phase I studies—namely, the use of normal, healthy controls as study participants. Safety, tolerability, and pharmacodynamics may differ between healthy controls and individuals affected with glaucoma. Further studies are warranted to assess whether tafluprost would be equally safe and well tolerated in patients with glaucoma.

CONCLUSIONS

In summary, tafluprost 0.0025% and 0.005% eye drops were generally well tolerated and safe. Tafluprost 0.005% reduced IOP significantly more, compared with placebo or latanoprost 0.005%. These data support further the testing of tafluprost as a new treatment for elevated IOP.

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