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REVIEW

Tafluprost: a Novel Prostaglandin Analog for Treatment of Glaucoma

Mina B. Pantcheva · Leonard K. Seibold · Nida S. Awadallah · Malik Y. Kahook

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ABSTRACT

Objective: The objective of this review is to evaluate the safety and efficacy of tafluprost, a fluoroprostaglandin receptor analog, for reduction of intraocular pressure in open angle glaucoma and ocular hypertension. ***Methods:*** A search of published literature was performed on the PubMed database using the search term "tafluprost." The literature search identified 48 publications, including clinical and preclinical studies, from 2003 to 2011. From these ressults, articles available in the English language and in full text were selected and systematically reviewed by the authors. ***Results:*** Recent studies have shown that tafluprost is an effective IOP-lowering medication. Evidence based medicine also reveals that tafluprost is safe and well-tolerated. Preservative-free tafluprost is as potent as the preserved formulation, but with fewer and milder ocular surface side effects. ***Conclusion:*** Since its introduction in 2008, initial studies have demonstrated that preserved and preservative-free tafluprost formulations have proven efficacy and safety in the treatment of glaucoma and ocular hypertension. Larger studies with longer follow-up are needed to assess long-term safety, efficacy, and tolerability compared with other prostaglandin analogs used for treating glaucoma.

Keywords: intraocular pressure, ocular surface, prostaglandin analog, tafluprost

Malik Y. Kahook (✉) · Mina B. Pantcheva · Leonard K. Seibold
University of Colorado School of Medicine, Ophthalmology Department, 1675 Aurora Court, Aurora, CO 80045, USA.
Email: malik.kahook@gmail.com

Nida S. Awadallah
Rose Family Medicine, 4545 East 9th Suite#010, Denver, CO 80220, USA

INTRODUCTION

Increased intraocular pressure (IOP) is considered a primary factor in the pathogenesis of glaucoma and is the only modifiable risk factor known at this time.[1-4] Prostaglandin (PG) analogs (PGA) are currently used as first-line therapy for the treatment of open angle glaucoma (OAG) and ocular hypertension (OHTN) because of their potent IOP-lowering efficacy, low likelihood of systemic adverse

effects, once-daily dosing, and good patient adherence. Tafluprost is a novel PGA with high affinity for the fluoroprostaglandin (FP) receptor $PGF_{2\alpha}$. Initial studies have demonstrated excellent IOP reduction in pre-clinical studies as well as in multiple clinical trials.[5-10] It has been approved for ophthalmic use in a number of markets worldwide. This review will focus on the efficacy and safety profile of tafluprost as well as the potential role of the preservative free tafluprost formulation in reducing long-term ocular side effects.

METHODS

The search of the PubMed database was performed using the search term "tafluprost." The literature search identified 48 publications from 2003 to 2011. Articles available in full text and in the English language were systematically reviewed by the authors and included in this review.

PHARMACOLOGICAL PROFILE OF TAFLUPROST

Tafluprost (1-methylethyl [5Z]-7-[(1R,2R,3R,5S) -2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclo-pentyl]-5- heptenoate) is a 16-phenoxy analog of $PGF_{2\alpha}$ with a 15,15-difluoro substitution.[6,11] It is an isopropyl ester that, like other PGA, is rapidly hydrolyzed by corneal esterases to the free acid of tafluprost, which is the active form. Because of its difluoro substitution, ketonization by 15-hydroxy-dehydrogenase (one of the major pathways involved in the metabolic degradation of PG) does not occur with this compound. Instead, the drug is metabolized only through beta-oxidation of the alpha-chain of the PG skeleton. Despite this lone pathway for metabolic degradation, tafluprost did not appear to accumulate in rat studies.[12] Tafluprost increases *in vivo* uveoscleral outflow as measured by fluorophotometry.[6] After both single and repeated topical dosing, the plasma concentration of tafluprost remains low. The active form, tafluprost acid, can be detected in plasma for up to one hour after topical administration, with a peak at 10 minutes.[10] Tafluprost has an affinity for the FP receptor that is approximately 12 times higher than that of the carboxylic acid of latanoprost, but with almost no potential to bind to other receptors.[6] In comparison, the affinity of travoprost for the prostanoid FP receptor has been reported to be 2.8 times as high as that of latanoprost.[13]

TAFLUPROST EFFICACY AND SAFETY - PRECLINICAL AND ANIMAL STUDIES

The IOP-lowering action of tafluprost has been demonstrated both in ocular normotensive monkeys and in laser-induced ocular hypertensive monkeys.[6] In both the ocular hypertensive and normotensive groups, single-dose applications of tafluprost (0.00002% to 0.0025%) induced a dose-dependent IOP reduction. In the normotensive monkeys, a statistically significant IOP reduction compared to vehicle was achieved with a single dose of tafluprost at doses of 0.0005% and 0.0025%. The IOP reduction of tafluprost at 0.0025% was significantly greater than latanoprost at 0.005%, while with tafluprost at 0.0005% it was almost equal to that of latanoprost in this group. When the normotensive monkeys received repeated doses of tafluprost (0.0015%, 0.0025%, or 0.005%) once-daily for 5 days, IOP-lowering was achieved on the first, third, and fifth days of administration, without an attenuation of efficacy over time. Similarly, 0.005% of latanoprost achieved IOP reduction at days 1, 3, and 5, however, IOP returned to baseline when measured at the trough time-point

(24 hours after drug administration) on each day. In contrast, when any concentration of tafluprost was administered, IOP levels at the trough-points of day 3 through 5 were significantly lower than those in the vehicle-treatment group.[6] These results suggest that the duration of action of tafluprost may be extended upon repeated dosing. Kurashima et al. tested 10 monkeys with a low susceptibility to latanoprost and first confirmed an inadequate reduction of IOP in response to treatment with the drug.[14] The monkeys were then switched to tafluprost therapy and the responses were compared. They demonstrated that the magnitude of IOP reduction induced by tafluprost 0.0015% (2.4 mmHg) was significantly greater than latanoprost 0.005% (0.4 mmHg) in all monkeys tested ($P<0.01$).[14]

A dose-dependent reduction of IOP with tafluprost was also demonstrated in the eyes of prostanoid FP-receptor deficient mice.[15] Tafluprost's effect on IOP was similar to that of travoprost, but stronger and more durable than that of latanoprost. In this animal model, Ota et al. also confirmed that tafluprost lowered IOP via prostanoid FP receptors, and found that part of the hypotensive effect may be related to FP receptor-mediated PG production and stimulation of PG E3 (EP3) receptors.[16] This IOP-lowering effect in mice was confirmed by Akaishi et al.[17]

Recent clinical studies have suggested that impaired blood flow to the optic nerve head (ONH) may contribute to glaucomatous optic neuropathy.[18] Blood flow to the ONH was significantly lower in patients with OAG compared to ocular hypertension patients or normal volunteers.[19,20] It has been suggested that a decrease in ONH blood flow is linked to the progressive visual field loss in glaucoma.[21,22] Izumi et al. noted that administration of tafluprost 0.0015% significantly increased retinal blood flow and blood velocity as measured by laser doppler velocimetry in cats.[23] This observation was then confirmed by Akaishi et al. who found that ONH blood flow increased in rabbit eyes after 28 days of treatment with any of the three $F_{2\alpha}$ prostaglandin analogs (tafluprost, latanoprost, or travoprost).[24] Using laser speckle flowgraphy, the effect of tafluprost (+11.9%) on blood flow was significantly greater than that seen with travoprost (+6.7%, $P=0.037$) and tended to be greater than that seen with latanoprost (+7.2%, $P=0.086$) at 60 min on day 28 post treatment.[24]

Dong et al. found that tafluprost induced concentration-dependent relaxation of precontracted isolated rabbit ciliary arteries, but by a mechanism that was independent of endothelial-derived factor.[25] They showed that the tafluprost-induced relaxation might be due, at least in part, to an inhibition of the capacitative entry of extracellular Ca^{2+}. An improvement in blood flow was demonstrated with $PGF_{2\alpha}$ analogs in a rabbit model of disturbed blood flow induced by administration of endothelin-1 (ET-1) into the vitreous.[26] Tafluprost had a longer-lasting inhibition of the ET-1-induced impairment of ONH blood flow than the three 15-hydroxyl-type $PGF_{2\alpha}$ analogs tested (15-OH tafluprost, travoprost, and latanoprost).

The authors speculate that these *in vivo* results were due to the di-fluorine at the carbon 15 position of tafluprost. The fluorine moiety imparts resistance to oxidation by the 15-hydroxyl prostaglandin dehydrogenase present in the ONH and blood, therefore making its observed inhibitory effect more prolonged than those of the 15-hydroxyl-type $PGF_{2\alpha}$ analogs. Tafluprost also increased ONH blood flow in both normal and experimental glaucomatous eyes in monkeys.[27] However, at this time we do not have sufficient means of reliably and reproducibly

measuring blood flow in human eyes and the potential beneficial role of ocular blood flow improvement by PG derivatives, including tafluprost, should be verified in the future.

There is evidence that tafluprost has some neuroprotective action as well. Kanamori et al. identified a direct antiapoptotic effect of tafluprost on cultured retinal ganglion cells and rat retinal ganglion cells after optic nerve crush. [28] For the *in vitro* model, where retinal ganglion cell apoptosis was induced by serum-removal or by glutamate exposure, tafluprost suppressed apoptosis in a dose-dependent manner, significantly reducing the number of caspase 3-positive cells ($P<0.05$) and suppressing intracellular Ca^{2+} levels evoked by exogenous glutamate. For the *in vivo* rat model of optic nerve crush, tafluprost increased the survival rate of ganglion cells in eyes treated for 14 days after optic nerve crush ($P=0.01$).[28] In a more recent study, commercially available preservative-free tafluprost was applied directly onto the surface of a rat retinal explant culture.[29] The authors noted a reduction of both neuronal and total cell loss from the retinal ganglion cell layer at 4 days *ex vivo*, compared to controls, although no effect was found after 1 week.[29]

One of the known adverse reactions to PG derivatives is pigmentation of the iris and/or eyelids. Work by Takagi et al. analyzed the potential melanogenesis effect of tafluprost *in vitro*.[6] Melanoma cells that had been incubated for 4 days in a medium supplemented with a high concentration of tafluprost failed to exhibit the elevated melanin content seen in cultures containing the same concentration of latanoprost.[6] The lack of reaction in the tafluprost-treated cells, despite the presence of such a reaction in the latanoprost-treated cells, may indicate that the incidence of iris or eyelid pigmentation will be lower with tafluprost, and if present, it will not be severe.

Perhaps the most distinguishing feature of tafluprost is that it is the first preservative-free PGA formulation. It has been speculated that removal of benzalkonium chloride (BAC), which helps in corneal penetration of less lipophilic medications, would reduce intraocular delivery, and therefore effectiveness.[30,31] However, the removal of BAC did not affect corneal penetration of preservative-free tafluprost in rabbits.[32] After the administration of a single topical dose (30 µl), the maximum concentrations at 45 minutes of tafluprost acid in aqueous humor were 4.50 ng/mL for preservative-free tafluprost and 3.99 ng/mL for preserved tafluprost. This may be due to the fact that tafluprost is a lipophilic prodrug ester with inherently high corneal permeability. *In vivo* and *in vitro* studies have shown that the preservative-free tafluprost causes less conjunctival damage than the preserved PG.[33,34]

In a conjunctival cell line, the application of preservative-free tafluprost showed significantly higher membrane integrity and lower pro-apoptotic and pro-oxidative effects compared to preserved latanoprost, travoprost, or bimatoprost.[33] Liang et al. assessed conjunctival and corneal reactions to preservative-free tafluprost, commercially available latanoprost, and BAC 0.02% following repeated applications to rabbits *in vivo*.[34] They found that both the preserved latanoprost and BAC induced greater expression of inflammatory markers and caused more ocular surface toxicity than the preservative-free tafluprost.

TAFLUPROST EFFICACY AND SAFETY - CLINICAL STUDIES

The pharmacodynamics, safety, and tolerability of tafluprost were assessed in two placebo-controlled phase I clinical trials.[8,9] In the first phase I study, tafluprost 0.0025% and

0.005%, latanoprost 0.005%, and placebo were administered to healthy volunteers for 7 days. The decline in IOP from baseline was 4.3 mmHg for tafluprost 0.0025%, 6.8 mmHg for tafluprost 0.005%, 5.3 mmHg for latanoprost, and 3.1 mmHg for placebo. The decrease in IOP values compared to baseline was significant for all treatment groups, and superior with tafluprost 0.005% compared with placebo, and for several time-points with tafluprost 0.005%, compared with latanoprost.[8]

In the second placebo-controlled phase I study, healthy volunteers were given sequential increasing doses of tafluprost, ie, 0.0001%, 0.0005%, 0.0025%, and 0.005%. For all doses, IOP reduction was present as compared with placebo. The effect was dose-dependent and significant for concentrations of 0.0005%, 0.0025%, and 0.005%. The effect was maximal at 12 hours after administration and lasted throughout the duration of treatment (2 days).[9] After a subsequent dose-response phase II trial in Japan, the therapeutic concentration of tafluprost was set at 0.0015%, which was not used in phase I studies.[11] The systemic safety was similar for tafluprost, latanoprost, and placebo when administered topically.[8,9] The investigators did not observe clinically significant changes in laboratory parameters, vital signs, or electrocardiographic parameters in any of the 49 participants throughout the course of the first phase I study.

The most common ocular side effect was ocular hyperemia. This was more frequent after administration of tafluprost in concentrations of 0.0025% or 0.005% than after administration of latanoprost 0.005%.[8] The incidence of photophobia was also greater in the tafluprost group than in the latanoprost group, however, this only occurred at doses greater than the currently available preparations, ie, 0.0015%. Similar observations were made in the second phase I study.[9] The authors stated that the overall rates of adverse effects were similar for the tafluprost 0.0001%, tafluprost 0.0025%, and latanoprost 0.005% groups, but rates of ocular hyperemia was significantly lower in eyes receiving latanoprost. All adverse events described in the first two phase I studies were mild to moderate and did not result in treatment discontinuation.

In a third phase I study evaluating the pharmacokinetics and efficacy of preserved and preservative-free tafluprost, Uusitalo et al. did not observe any significant differences in pharmacokinetic parameters between the formulations after single or repeated dosing.[10] Ocular hyperemia occurred with the same frequency in both groups, but was predominantly of moderate severity in eyes treated with preserved tafluprost, compared to only mild severity with the preservative-free formulation. The authors assessed the conjunctival hyperemia using reference photographs and a five-step scale; half steps were allowed to refine the scale.

In a randomized, double-masked, controlled, multicenter, multinational phase II study, Traverso et al. assessed the duration and stability of the IOP-lowering effect and tolerability of tafluprost 0.0015% compared with latanoprost 0.005% in patients with primary open-angle glaucoma, exfoliation glaucoma, or OHTN.[35] The maximum reduction of IOP was reached by day 7 of treatment and sustained until day 42. The tafluprost 0.0015% decreased IOP 9.7±3.3 mmHg from baseline, while latanoprost 0.005% lowered IOP by 8.8±4.3 mmHg. The overall treatment group difference was 0.17 mmHg (95% CI –1.27-1.61; P=0.811).

The effect of tafluprost 0.0015% on IOP and the safety of this medication were demonstrated in a randomized, parallel-group, double-masked European phase III study conducted in 49 centers in eight countries for up to 24 months.[36] This study compared the efficacy and safety profiles

of preserved tafluprost 0.0015% and latanoprost 0.005% in 533 patients with OAG, including pigmentary and exfoliative glaucoma, and OHTN. After 24 months, the mean decrease in IOP from baseline was 7.1 mmHg (29.1%) in the group treated with tafluprost and 7.7 mmHg (32.2%) in the group treated with latanoprost. This difference was clinically small (0.6 mmHg) and the noninferiority of tafluprost to latanoprost over all diurnal IOP measurements was shown with analysis of variance, and almost reached with analysis of covariance (upper limits of the 95% CI 1.38 and 1.52 for the overall period, respectively). The noninferiority limit was 1.5 mmHg.

Both drugs were well tolerated. Reported adverse events were mild to moderate. Nonocular adverse events were reported in 133 (50.4%) patients treated with tafluprost, and in 114 (43.2%) patients treated with latanoprost. Of these, eleven participants in the tafluprost group and nine in the latanoprost group were considered to be related to treatment. Ocular adverse effects were reported by 48.1% of patients in the tafluprost group and by 44.3% of patients in the latanoprost group. The most frequently reported adverse effect was conjunctival hyperemia. The stimulating effect on eyelash growth was absent or mild in 90% of patients after 24 months in both the tafluprost and latanoprost groups. More cases of iris pigmentation were reported in the latanoprost group (28%) than in those treated with tafluprost (26.1%), but these differences were not significant.[36]

The diurnal IOP-lowering efficacy and safety of travoprost 0.004% and tafluprost 0.0015% in 48 patients with primary OAG or OHTN was compared in a randomized, double-masked, active-controlled, crossover trial for 6 weeks with each medication.[37] The 12-hour mean diurnal IOP was significantly lower with travoprost than with tafluprost (16.9 mmHg versus 17.5 mmHg, respectively; P=0.01). Neither therapy produced a significant increase from baseline in light sensitivity, blurred/dim vision, stinging/burning, foreign body sensation, or pain. Hyperemia was increased with both therapies ($P \leq 0.01$). Investigator-observed hyperemia was also significantly increased from baseline for both travoprost (0.26±0.56, $P<0.01$) and tafluprost (0.42±0.54, $P<0.01$), although the increase with travoprost therapy was significantly smaller than with tafluprost ($P<0.01$).[37] The study provided only 6 weeks of treatment with each study medication, thus it could not identify any long-term efficacy and safety differences between travoprost and tafluprost.

The efficacy and safety profile of preserved and preservative-free tafluprost was also compared in a phase III crossover study.[7] In this group of 43 patients with OAG, the authors showed that both formulations demonstrated a clear reduction of IOP within 1 week, which was sustained at week 4. The overall difference between the two formulations was not statistically significant.

The preservative free formulation of tafluprost appears to be a good alternative for patients exhibiting ocular surface side effects while receiving other PG formulations. In an effort to evaluate this, Uusitalo et al. investigated the hypotensive effect and tolerability of preservative-free tafluprost in 158 patients with OAG and OHTN who were exhibiting ocular surface side effects during latanoprost treatment.[38] Twelve weeks after switching from preserved latanoprost to preservative-free tafluprost, IOP remained at the same level. Mean IOP values were 16.8±2.5 mmHg at baseline on latanoprost, and 16.2±2.4 mmHg, 16.4±2.5 mmHg, 16.4±2.7 mmHg at 2, 6, and 12 weeks of treatment with preservative-free

tafluprost, respectively. Compared to baseline, the IOP levels were similar, but statistically significantly lower during treatment with preservative-free tafluprost (P=0.002; 0.018, and 0.049, respectively). The number of patients with objective ocular side effects (conjunctival hyperemia, corneal, and conjunctival fluorescein staining, etc.) was reduced by approximately 50% after switching the drugs. The same was reported for ocular symptoms including itching, tearing, irritation, burning, stinging, and foreign body sensation. After 12 weeks of tafluprost preservative-free treatment, fluorescein break-up time increased from 4.5±2.5 seconds at baseline to 7.8±4.9 seconds (P<0.001).

Results of impression cytology samples revealed there was a statistically significant reduction of abnormal conjunctival cells based on HLA-DR and Mucin-5AC expression. These observations may indicate a less harmful impact of preservative-free tafluprost on the conjunctiva than preserved latanoprost. Furthermore, in a multicenter, observational, open-label study of 544 glaucoma patients, Hommer et al. showed that preservative-free tafluprost provided further IOP reduction in patients with poor IOP control and/or poor tolerance of their medication prior to tafluprost use.[39] IOP reduction was achieved for patients being switched from other monotherapies, including β-blockers, carbonic anhydrase inhibitors, and other PGA to a monotherapy with preservative-free tafluprost. Patients also demonstrated a decrease in signs and symptoms of ocular side effects.[39]

In a recent prospective, multicenter, noninterventional, observational, open-label study conducted in Germany between July 2009 and February 2010, patients with glaucoma or OHTN were followed after switching to once-daily therapy with preservative-free tafluprost 0.0015%. Patients were selected once investigators determined a need for a change of medication, an add-on therapy, or who were treatment naïve. Subjects were then followed for 6 to 12 weeks after they were switched to once-daily therapy with preservative-free tafluprost 0.0015%. At the final visit of 6 to 12 weeks, the mean IOP value for all patients was significantly lowered from 19.5±4.4 mmHg at baseline to 16.4±2.9 mmHg on tafluprost (P<0.001). Preservative-free tafluprost also significantly lowered IOP in all monotherapy subgroups including beta blockers (n=307), carbonic anhydrase inhibitors (n=158), PGA (n=447), and treatment-naïve patients (n=440). At baseline, tolerability of the prior treatment was rated as "very good" and "good" by 28.3% of the patients; 38.4% of patients had rated the tolerability as "less satisfactory," and 18% as "not acceptable." The tolerability had improved after the change to preservative-free tafluprost with a total of 85.7% of patients rating the tolerability as "very good" and "good."[40] The observed IOP reduction in these observational open-label studies may be a result of increased compliance due to the improvement of the subjective symptoms and clinical signs. Also, regression to the mean cannot be ruled out since a control group was not used.

CONCLUSION

Tafluprost appears to be a promising new alternative in the treatment of glaucoma. Clinical trials have demonstrated good IOP lowering efficacy and safety profile of this novel agent. The available preservative-free formulation appears to provide an effective alternative to patients intolerant of preserved PGA or other medications, by decreasing signs and symptoms of ocular side effects. Further studies are needed to confirm tafluprost's efficacy and tolerability in clinical practice and establish its role among other PGAs available for the treatment of glaucoma.

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