DRUG REVIEW

Tafluprost: Adding New Dimension to Antiglaucoma Therapy

Harmanjit Singh, Harish Kumar, Pugazhenthan Thangaraju, Bikash Medhi

Introduction

Glaucoma is the second leading cause of preventable blindness worldwide. In 2010 worldwide approximately 60.5 million people were suffering from primary open angle glaucoma (POAG) and angle closure glaucoma (ACG) and this number is estimated to be increase to 79.6 million by 2020 (1).

Prostaglandins (PG) analogues occupy centre stage among glaucoma medications because they are more effective in lowering intraocular pressure (IOP) and have considerably fewer systemic side effects. Currently, four different types of PG analogues-isopropyl unoprostone, latanoprost, travoprost, and bimatoprost are used for the treatment of glaucoma. These four PGs are superior to beta-adrenoceptor antagonists in terms of lowering IOP, and they have no severe side effects during long-term clinical use. To minimize the side effects of long-term treatment, preservative-free preparations and alternative preservatives have been developed and reported to have a lower rate of side effects (2,3).

Tafluprost is a novel prostaglandin that has been approved for ophthalmic use in a number of markets worldwide. It is highly selective for the prostaglandin FP-receptor. The drug is the first and only prostaglandin that is available in a preservative-free (PF) formulation for the treatment of patients with glaucoma and ocularHypertension (4). This may be important because special attention has been paid to the cytotoxicity of benzalkonium chloride (BAK), which is widely used in glaucoma preparations as a preservative. BAK is pro-apoptotic, pro-inflammatory and causes a damage of the tear film by emulsification of the lipid layer. A complete loss of conjunctival goblet cells was also reported in different studies. On the ocular surface of patients with glaucoma, BAK induced complex inflammatory mechanisms, causing both allergy and toxicity. These changes cause irritation, ocular discomfort, and subjective visual complaints. Therefore, PF-medications may be beneficial for many glaucoma patients (5,6,7).

Tafluprost is a 16-phenoxy analog of PGF2 alpha, with a 15,15-difluoro substitution. It is presently available in two formulations, i.e, with BAK (TaprosR in Japan) and PF (TaflotanR in Europe), both in 0.0015% concentrations (8-11).

It differs from the other prostanoids because it possesses two fluorine atoms at the carbon 15 position, instead of the hydroxyl group present in latanoprost, travoprost, and bimatiprost. It is an isopropyl ester (AFP-168) and, like other prostaglandin analogues, is rapidly hydrolyzed by corneal esterases to the free acid of tafluprost (AFP-172), which is its active form. It is a very potent FP receptor agonist, with a Ki of 0.4b nM. Its affinity for the human prostanoid FP receptor is 12 times that of the carboxylic acid in latanoprost and 1700 times that in unoprostone. It also has a 126-fold higher affinity for FP receptors than for EP3 receptors (4, 12,13). After either single or repeated topical dosing, the plasma concentration of tafluprost is low. Moreover, it is cleared rapidly from the circulatory system. Its active form, i.e, tafluprost acid, can be detected in plasma for up to one hour after topical administration, with a peak at 10 minutes (14).

Mechanism of Action of Tafluprost

Tafluprost has demonstrated affinity for the prostanoid FP receptor that seems to be greater than for other PGs and almost no affinity to bind to other receptors. It reduces IOP by increasing the uveoscleral outflow of aqueous humor. Further, it may relax ciliary artery in smooth muscler due to inhibition of calcium from extra-cellular spaces. The presence of esterase activity in the cornea and sclera capable of hydrolyzing the PG derivatives to the corresponding acids for uptake during absorption into aqueous humor is also well established (15), This pro-drug ester allows for greater delivery of carboxylic acid (active) to the aqueous humor (3, 16).

Animal studies

This drug has shown greater efficacy than other available PG analogues in various animal models of glaucoma. In a study done on mice by Ota T *et al* (17),

From the Postgraduate Department of Pharmacology, PGIMER, Chandigarh-160012 India
Correspondence to : Dr. Bikash Medhi, Additional Professor, Department of Pharmacology, PGIMER, Chandigarh-160012 India

Tafluprost 0.005% significantly decreased IOP more than 0.005% latanoprost at 3, 6, and 9 hours or 0.12% unoprostone at 2, 3, and 6 hours.

Kanamori *et al* (18) reported neuroprotective effects of tafluprost in a rat model in which retinal ganglion cell apoptosis was induced by serum-removal or by glutamate exposure. Tafluprost suppressed the apoptosis in a concentration-dependent manner. They also noted that in a rat model of optic-nerve crush, treatment with tafluprost ophthalmic solution increased the survival rate of retinal ganglion cells.

The IOP-lowering activity of tafluprost has been demonstrated both in ocular normotensive monkeys and in laser-induced ocular hypertensive monkeys by Takagi *et al.*(5). In the former the maximal IOP reductions achieved with a single dose of tafluprost (0.00002 to 0.0025%) were dose-dependent, with statistical significance being reached at doses of 0.0005 and 0·0025%, and the potency of tafluprost at 0·0005% was almost equal to that of latanoprost at 0·005%. Similarly, in laser-induced ocular hypertensive monkeys, single-dose applications of tafluprost (0.00002 to 0.0025%) induced a dose-dependent IOP reduction. When normotensive monkeys received repeated doses of tafluprost (0.0015%, 0.0025%, or 0.005%) once daily for 5 days, this drug exhibited IOP-lowering effects not only on the first day, but also on the third and fifth days of administration. These results suggest that the duration of action of tafluprost may become longer upon repeated dosing.

In a study, the conjunctival and corneal reactions of commercially available solution of latanoprost and preservative-free tafluprost was compared in rabbits. The rabbits received 50 ml of phosphatebuffered saline (PBS), PF-tafluprost 0.0015%, latanoprost 0.005% or benzalkonium chloride (BAK) 0.02%; all solutions were applied at 5 min intervals for a total of 15 times. The ocular surface toxicity was investigated using slit-lamp biomicroscopy examination, flow cytometry (FCM) and on imprints for CD45 and tumour necrosis factor-receptor 1 (TNFR1) conjunctival impression cytology (CIC) and corneal in vivo confocal microscopy (IVCM). Standard immunohistology also assessed inflammatory apoptotic cells. Clinical observation and IVCM images showed the highest ocular surface toxicity with latanoprost and BAK, while PF-tafluprost and PBS eyes presented almost normal corneoconjunctival aspects. Th e results showed a lower expression of CD45+ and TNFR1+ and better corneoconjunctival tolerance in PF-tafluprost group than latanoprost or BAK instilled groups (8).

The interactions of rabbit ciliary arteries with tafluprost have been studies by Dong and co-workers (10). This group showed that tafluprost caused a concentration dependent relaxation of ciliary artery segments.

Clinical studies

Sutton et al 13: The pharmacodynamics, safety, and tolerability of tafluprost in healthy volunteers were assessed in this clinical, masked, placebo-controlled PhaseI study. Tafluprost 0.0025% and 0.005%, latanoprost 0.005%, and placebo were given for seven 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 was superior with tafluprost 0.005% to values with placebo and latanoprost 0.005%.

Traverso *et al* (19) This was a randomized, double-masked, active-controlled, parallel-group, multinational, and multicenter phase II study. Patients received either tafluprost 0.0015% (n = 19) or latanoprost 0.005% (n = 19), both once daily. The extent and duration of action of the IOP-lowering effects at Day 42 and Day 43 were the primary efficacy endpoints. The overall treatment group difference was 0.17 mm Hg (95% confidence interval -1.27 to 1.61; P = 0.811). The IOP-lowering effect was maintained for nearly 24 h after the last dose in both groups.

Uusitalo H *et al:* (20) A double-blinded, active-controlled, parallel-group, multinational, multicentre phase III study conducted at 49 centres in 8 countries where long-term efficacy and safety of tafluprost 0.0015% was compared with latanoprost 0.005% eye drops in patients with OAG or ocular hypertension. The eligible patients were assigned to treatment administered once daily at 20:00 hrs for up to 24 months. Change from baseline intraocular pressure (IOP) was the primary efficacy variable. Both tafluprost and latanoprost were preserved with BAK chloride. Although the IOP-lowering effect during the study was slightly larger with latanoprost, this difference was clinically small and the noninferiority of tafluprost to latanoprost over all diurnal IOP measurements was shown.

Erb *et al* (21): Noninterventional and observational study where the efficacy, local tolerability, and safety of preservative-free tafluprost was evaluated in patients with ocular hypertension and glaucoma . IOP readings were recorded at baseline and 6-12 weeks after changing medical treatment to or initiating treatment with PF-tafluprost once daily. Local comfort was determined using a five-point scale (very good, good, satisfactory, less satisfactory, not acceptable) before and after the change of medical treatment. Data from 2123 patients with glaucoma or ocular hypertension were considered for the final evaluation. In all patients PF- tafluprost 0.0015%

lowered IOP from 19.5±4.4 mmHg (baseline) to 16.4±2.9 mmHg after 6-12 weeks. It also significantly lowered the IOP in all monotherapy subgroups: treatment-naïve patients (n=440). Local comfort was rated as "very good" or "good" by 85.6% of patients at the final visit (P<0.001). Only few adverse events occurred during the treatment period: 18 patients (0.8%) discontinued medical treatment with PF- tafluprost due to local intolerance.

Hommer *et al:* (22) Non-interventional, prospective, multi-centric, observational, open label study, where the efficacy, tolerability and safety of the PF- tafluprost 0.0015% were investigated for the treatment of patients with glaucoma or ocular hypertension. 118 patients were treated with a monotherapy with preserved formulations of latanoprost, travoprost or bimatoprost IOP readings were recorded for each eye at baseline, 4-6 weeks, and 12 weeks after changing medical treatment to PF-tafluprost once-daily. In these patients with prior PGA monotherapy IOP decreased significantly from at treated baseline to at final visit on tafluprost. The number of patients with moderate and severe hyperemia decreased from 51 (43.2%) at baseline to 2 (1.9%) at final visit.

Sutton *et al* (23): Placebo-controlled Phase I study where healthy volunteers were given sequential ascending doses of tafluprost, ie, 0.0001%, 0.0005%, 0.0025%, and 0.005%. For all these doses, a decreasing IOP effect 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.

Traverso *et al* (24): Randomized, double-blinded, controlled, multicenter, multinational Phase II study where the duration and stability of the IOP-lowering effect and tolerability of tafluprost 0.0015% were assessed compared with latanoprost 0.005% in patients with POAG, exfoliation glaucoma, or ocular hypertension. They observed that maximum reduction of IOP was reached by day 7 of treatment and sustained until day 42 in both groups. The overall treatment group difference was 0.17 mm Hg (95% confidence interval -1.27 to 1.61; P = 0.811). Most adverse events were ocular and were similar in frequency and severity between groups.

Pantcheva MB *et al* (25): They evaluated the safety and efficacy of tafluprost in a systematic review. The literature search identified 48 publications, including clinical and preclinical studies, from 2003 to 2011. It shown that tafluprost is an effective IOP-lowering medication. Evidence based medicine also reveals that tafluprost is safe and well-tolerated. PF- tafluprost is as potent as the preserved formulation, but with fewer and milder ocular surface side effects .

Egorov *et al* (26): Randomized, double-masked, parallel-group, multinational and multicenter 12-week phase III study where the efficacy and safety of tafluprost (0.0015%) as an adjunctive therapy to timolol, were evaluated in patients with OAG or ocular hypertension, uncontrolled by timolol monotherapy. They concluded that as adjunctive therapy to timolol, tafluprost achieved a significant and consistently greater reduction in IOP compared with vehicle, and was well tolerated.

Chabi *et al* (27): Randomized, double-masked, multicenter clinical trial, compared the efficacy and safety of the PF-tafluprost with PF-timolol in patients with OAG or ocular hypertension. They concluded that the IOP-lowering effect of PF tafluprost was noninferior to that of PF timolol and PF tafluprost is an efficacious and well-tolerated ocular hypotensive agent.

Safety and Tolerability

Generally, tafluprost is well tolerated. The most common adverse effect reported in various trials is ocular hyperaemia (more frequent concentrations of 0.0025% or 0.005%). A slight overall tendency towards corneal thinning is observed in some patients. A PF solution of tafluprost has reduced toxicity in human conjunctival epithelial cell lines when compared with preserved latanoprost, travoprost, and bimatoprost. Tafluprost had low proapoptotic/pro-oxidative effects in vitro when compared with preservative-containing formulations (25, 26). In a study, patients with poor local tolerance of their medications noticed improvement of subjective symptoms and clinical signs after changing their therapy to PF-tafluprost 0.0015% (28). Other adverse effects are stinging, ocular pruritus, increased darkening or growth of eyelashes, and darkening of eyelids, as well as irreversible brown pigmentation of the iris (29).

Conclusion

The preservative containing tafluprost has definite advantages over the preservative containing prostaglandins analogues. There is a better safety and tolerability over the conventional preparations because many of the adverse drug reactions occur due to the preservative content of the solution. In various studies, there was equal or better efficacy than the conventional PG analogues like latanoprost. A change of medical therapy to PF tafluprost may be beneficial, especially for patients with subjective ocular symptoms and patients with sensitive or dry eyes but also for patients who are not responding adequately to other monotherapy treatment regimens. The results of existing clinical studies of tafluprost use are promising but we need additional experience with the drug to establish its long term benefits in patients of glaucoma.

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