Expert Opinion

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Tafluprost for glaucoma

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Introduction: Lowering intraocular pressure (IOP) is, at present, the only therapeutic approach to the treatment of glaucoma. Good compliance is essential in every chronic therapy; therefore, the development of IOP-lowering eye drops that are well tolerated and have an easy administration schedule is essential for the treatment of glaucoma. Prostaglandins are a first-choice drug class for the treatment of glaucoma.

Areas covered: This review provides a background on tafluprost, a newly synthesized prostaglandin analogue, and summarizes the existing data on its efficacy and safety, including comparative data with the other prostaglandin derivatives now available on the market. A review of the literature was performed.

Expert opinion: Current research focuses not only on the efficacy of the drugs but also on their tolerability. The importance of obtaining good compliance by the patient is increasingly relevant; therefore, new formulations are studied to provide fewer side effects and an easier schedule. Tafluprost is a new prostaglandin analogue that has been marketed in some European countries and in Japan for more than 2 years and was recently (July 2009) approved in 21 countries. Besides a well-demonstrated IOP-lowering effect, tafluprost is the first topical prostaglandin available as a preservative-free formulation.

Keywords: glaucoma, IOP, preservative-free, prostaglandin, topical therapy

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1. Introduction

The ultimate goal for glaucoma treatment is to slow the rate of progression of the disease so that it will not interfere with patients' ability and quality of life during their lifetime. Lowering intraocular pressure (IOP) is at present the only therapeutic approach to the treatment of glaucoma. Since the use of pilocarpine eye drops in the late 1870s, academic researchers and pharmaceutical companies have attempted to discover new drugs with more potent, prolonged and safer IOP-lowering effects [1].

Glaucoma has been treated pharmacologically for more than 140 years. Today there are four main classes of topical ocular hypotensive drugs used to lower IOP. These include: beta-blockers (beta-adrenergic antagonists); cholinergics; carbonic anhydrase inhibitors; alpha-2 agonists; and prostaglandin analogues. Each of these drugs can be effective at lowering IOP in the majority of patients, but there is considerable variation in efficacy among them.

Reducing IOP is at present the only proven strategy to slow down visual field loss in glaucoma patients [1]. The idea of using prostanoids as ocular hypotensive agents in the treatment of glaucoma was first proposed by Camras and Bito [2].

Several synthetic prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogs with potent and long-lasting IOP-lowering properties are widely used in glaucoma and ocular-hypertension therapy.

Prostaglandin analogs, as a class, reduce IOP by 20 – 33%, depending on the clinical study [3-5]. Four prostaglandins – latanoprost, bimatoprost, travoprost and tafluprost (**Box 1**) – are now available as topical therapies. There is no significant difference among them in terms of how much each lowers IOP. Because prostaglandins require only once-daily dosing, they have generally been associated with

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Box 1. Drug summary.

Drug name (generic)	Tafluprost 0.0015%
Phase	Commercialized
Indication	Open-angle glaucoma/ocular hypertension
Pharmacology description/mechanism of action	Selective agonist for the prostanoid FP receptor Administered as prodrug ester (AFP-168; to enhance corneal penetration). The molecule is hydrolyzed by corneal esterases and delivered as the active carboxylic acid form, AFP-172) in the aqueous humor
Route of administration	Eyedrops
Chemical formula	AFP-168 (1-methylethyl (5Z)-7-[91R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5-heptenoate)
Pivotal trial(s)	Many clinical Phase I, II and III studies have been conducted so far. Traverso *et al.* studied the duration and stability of intraocular-pressure-lowering effect and tolerability of taluprost compared with latanoprost [68]

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greater ease of use and wider acceptance by patients. They have also shown fewer systemic side effects compared with other agents, although ocular side effects can be bothersome for many patients. All have been reported to cause variable degrees of conjunctival hyperemia, increased pigmentation of the iris and of the periocular skin, and increase in the length, number and pigmentation of the lashes [6,7]. Overall, the rate of discontinuation for patients using prostaglandin analogs may range from 50 to 70% over 180 days [8]. Schwartz [9] and Reardon *et al.* [10] have both proposed that this rate of discontinuation is not associated with the patient's ability to pay for the medications but probably is largely a result of the patient either not liking the dosing regimen, or complaining of adverse effects associated with the drug itself. Hyperemia is the most common side effect associated with the use of topical ocular prostaglandins and its incidence varies between different prostaglandin analogs [6]. The condition has been reported to occur less frequently among patients treated with latanoprost [11]. However, in a recent study Zimmerman *et al.* reported that prostaglandin-induced hyperemia was not the most common reason given by physicians for switching medication as 43% was due to lack of efficacy and 19% related to adverse events [12]. Overall, latanoprost seems to allow for a greater persistence than other topical hypotensive drugs [13]. Data from Reardon *et al.* showed that patients treated with timolol and bimatoprost were 37 – 72% more likely to discontinue therapy, respectively, if compared with latanoprost, and those treated with dorzolamide were 58% more likely to discontinue/change treatment [10].

In fact, a significant percentage of patients with glaucoma have a poor track record for using their ocular hypotensive drugs as prescribed by their physicians, regardless of which product they have been given [14]. Reasons for this poor compliance include side effects of the drug and the inconvenience of having to instill eye drops, especially if multiple times, each day. It is also disconcerting that many patients, particularly those with early-stage disease, which is often asymptomatic, do not consider glaucoma as a condition that threatens their vision [15]. Evidently there is insufficient information on how serious the outcome might be if the disease is left untreated. For most patients, regular and consistent use of these products involves a balancing act: finding a drug that provides the greatest reductions in IOP, the fewest side effects and the greatest ease of daily dosing.

A recent study of 83 patients pointed out that the occurrence of adverse events was the third cause of poor compliance [16]. A study of 13 977 patients pointed out that patients on topical prostaglandins who considered every side effect a relevant problem, had a lower compliance. The same study stated that most of the ophthalmologists considered side effects as a great issue for compliance [17]. Recent research has focused on products that do not interfere with the homeostasis of the ocular surface, in order to reduce the damages and the complaints of patients on chronic therapy regimen.

The toxic effect of preservatives on the ocular surface was confirmed by different studies. Conjunctival hyperemia [18], cellular apoptosis [19], ocular surface disease [20] and inflammatory cell infiltration of the conjunctiva were found in patients that had been on chronic hypotensive therapy for several years. The exact pathological mechanism causing this alteration was not found. Benzalkonium chloride (BAK) is a widely used preservative in ophthalmic formulations, although its toxicity was proved in experimental settings [21] and in animal [22] and clinical studies [23].

2. Overview of the market

Several epidemiological studies have demonstrated that patients on local IOP-lowering therapies complained about local discomfort [24,25]. Such discomfort is one of the most common causes of request for an ophthalmological consultation. The occurrence of ocular surface disease

(OSD) may be related to different factors, such as age, sex, race, the presence of blepharitis and the use of preserved eye drops [26,27]. Glaucoma patients are at risk for OSD because of the chronic use of preserved eye drops for many years; this is particularly evident as the patient gets older [28]. As with all patients affected by OSD, signs and symptoms are not always related and many glaucomatous patients who complain of dry eye symptoms do not have any measurable damage, and vice versa [29].

The symptoms may be related either to the instillation or to the period between the different instillations. Stinging and burning are common immediately after instillation of the eye drops. Twenty-five per cent of patients complained of the occurrence of side effects such as 'pain' immediately after the start of the therapy. The percentage rises to 40% if the symptom described is 'burning' that might also cause tearing. The latter is not only to be considered a side effect causing discomfort, but also a possible cause of impaired drug absorption, because of the related 'washout'. Other common symptoms are dry-eye sensation and itching of the palpebral margin. Recently, Leung *et al.* developed a questionnaire based on the Ocular Surface Disease Index (OSDI) to study the dry eye in glaucomatous patients [28]. In this study, 59% of the patients complained of dry-eye symptoms in at least one eye and 27% of the symptoms were referred to as 'severe'. Sixty-five per cent of the patients showed a change in the quality of the tear, and 35% showed a severe reduction of the quantity of tear production as measured by a Shirmer test. Twenty-two per cent of the patients were positive to coloration with lissamine green, showing a loss of epithelial cells.

Conjunctival hyperemia related to topical prostaglandin application is usually considered disagreeable by the patient. It is caused by a local vasodilatation and its gravity is related to the compound and to individual reactivity [30]. Usually the degree of hyperemia is apparently more severe than the symptoms (burning, stinging and itching).

3. Allergic reactions

3.1 Allergic reactions to antiglaucoma eye drops: specific reactions to active compounds

Topical IOP-lowering drugs can cause different reactions on ocular structures, especially on the ocular surface. Proper allergic reactions can be clinically serious; however, their incidence is definitely lower than the nonallergic alterations caused by the chronic use of such drugs. All in all they are rarely reported in clinical studies, because of their rarity, especially during the first months. The incidence of proper allergic reactions is very different, depending on the compound. Immediate allergic reactions are less frequent with timolol than with other hypotensive drugs [31]. Some authors reported an incidence of 1.5% of allergic reactions with latanoprost, when used as a second-line therapy [32]. Allergic reactions with brimonidine are reported to be between 4.2 and 25.7% [33], whereas they significantly drop when a combination of brimonidine and timolol is used [34].

Severe periocular dermatitis, possibly associated with atypical likenoid reactions were reported associated with the use of dorzolamide, even months after the beginning of the therapy [35]; the incidence of this type of hypersensitivity reactions are overall quite uncommon [36].

3.2 Allergic reactions to antiglaucoma eye drops: specific reactions to benzalkonium chloride

Beside the allergic reactions caused by the active compounds, preservatives might trigger an inflammatory response. There is a large body of evidence from experimental and clinical studies showing the toxic effect of benzalkonium chloride (BAK). Quaternary ammoniums, such as BAK, are most commonly associated with irritant toxic reactions (8% in OVID and PubMED based researches), whereas the organomercurials, such as thimerosal, and the alcohols, such as chlorobutanol, have the highest associations with allergic responses (respectively 19% of OVID and 14%of PubMED-based research and 20% of OVID and 11% of PubMED-based research), although for alcohols it is more an irritant effect; whereas the organomercurials seem truly to interact with the immune system as neoantigens [37]. The mechanism causing tear film instability, loss of globlet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier and damage of deep ocular tissues are far from being fully elucidated, but the involvement of immunoinflammatory reactions was proposed. The release of proinflammatory cytokines, apoptosis, oxidative stress as well as direct interactions with the lipid layer of the tear film and cell membranes are well established [38].

4. Higher rate of surgery failure

Several authors found a correlation between chronic topical long-term therapy and a higher rate of bleb failure after surgery [39,40]. Immediately after surgery fibroblasts tend to proliferate, to repair the incised tissues, thus reducing the filtration of aqueous humor to the subconjunctival space. An increase in inflammatory response leads to recruitment of fibroblasts that produce extracellular matrix. Long-term therapy with preserved local hypotensive drugs leads to conjunctival migration of macrophages and lymphocytes.

The inflammatory response was confirmed by the expression of HLA-DR and of adhesion molecules ICAM-1 and by overexpression of receptors for chemokines CCR4 and CCR5 [41]. The inflammatory reaction of the conjunctiva in glaucomatous patients seems to be related to the number of eye drops instilled and the duration of the therapy [42]. It was hypothesized that toxicity related to preservatives plays a relevant role in the conjunctival cicatricial response after surgery [43]. It seems therefore reasonable to try using preservative-free eye drops for glaucoma patients, especially if a surgical filtering procedure is a possibility.

The Blue Mountains Eye Study demonstrated that topical therapy also increases the incidence of cataract (OR = 1.90, 95% CI) [44].

It is not known whether this effect is due to the active molecule or to the preservatives, or both.

5. Introduction to the compound

Prostaglandin derivatives exert ocular-hypotensive effects through stimulation of prostanoid receptors and possibly by activation of signal-transduction systems such as intracellular Ca^{2+} and cyclic AMP [45]. Because of their potent, long-lasting ocular hypotensive effect and minimal systemic side effects, compounds acting on the prostanoid receptors are widely used in glaucoma therapy. Clinical use over several years has revealed the existence of patients who do not respond well to $PGF_{2\alpha}$ derivatives [46,47].

However, local side effects, such as pigmentation of the iris [48-50], the eyelid and/or periocular skin [51] and abnormal eyelash growth [52] have been widely reported. The $PGF_{2\alpha}$-derivative-induced eye color change is most likely related to an increased amount of melanin within iris stroma melanocytes [53].

5.1 Chemistry

AFP-168 (tafluprost; **Box 1**), 1-methylethyl (5Z)-7-[1R,2R, 3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5-heptenoate is a newly synthesized $PGF_{2\alpha}$-analog. It is a prodrug ester that facilitates corneal penetration and allows delivery of the active carboxylic acid form (AFP-172) to the aqueous humor, a similar situation to that seen with $PGF_{2\alpha}$-isopropyl ester and other ocular hypotensive derivates of $PGF_{2\alpha}$, such as latanoprost [54]. Esterification of the carboxyl group on the α-sidechain of these prostaglandins greatly enhances their penetration into the cornea, and the presence of esterase activity in the cornea and sclera capable of hydrolyzing these derivatives to the corresponding acids' uptake during absorption into aqueous humor is also well established [55]. The binding profile of tafluprost acid is that of a selective agonist for the prostanoid FP receptor [56]. The presence of two fluorine atoms in position 15 in the β-chain of the prostaglandin structure may bestow a more potent affinity for the prostanoid FP receptor [54]. The mechanism underlying the IOP-lowering effect of tafluprost was investigated in ocular normotensive monkeys and an increased uveoscleral outflow was detected. As for other $PGF_{2\alpha}$ analogues, a small decrease in the conventional outflow was detected, presumably due to rerouting of flow to the uveoscleral pathway [54].

5.2 Pharmacodynamics

The pharmacological efficacy of antiglaucoma agents applied topically to the eye is dependent on their ability to penetrate the cornea and access the anterior ocular tissues, particularly the iris and ciliary body, which is the presumed target of action. In the case of $PGF_{2\alpha}$ analogs, esterification of the prostaglandin α-chain carboxyl group sufficiently increases the lipophilicity of the molecule for it to traverse the cornea and/or sclera, where it is enzymatically hydrolyzed back to active acid form for delivery to the ocular tissues and fluids [57]. Recently, the efficacy of 15,15-difluorinated $PGF_{2\alpha}$ ocular hypotensive agent tafluprost as a prodrug for tafluprost acid has been tested on albino rats after ocular administration [58].

Tafluprost acid showed a potent affinity for the protsanoid FP receptor, and its affinity was greater than that of PhXA85, a carboxylic acid of latanoprost, or unoprostone. The binding affinity of tafluprost acid was 126 times higher for the prostanoid FP receptor than for EP_3 receptor [59]. The stimulatory effects on melanin content of a carboxylic acid of latanoprost on cultured melanoma cells [60] were not detected for 15,15-difluoroderivattives. The mechanism related to this is still unknown, but the lack of stimulatory effect on melanin content in cultured cells may be related to a lower rate of iris and periocular pigmentation when applied topically *in vivo* [54]. To asses these effects on melanin, additional studies are warranted.

5.3 Pharmacokinetics and metabolism

The pharmacokinetics and metabolism of the drug were studied accurately [61,62].

The prodrug was proved to be rapidly and completely hydrolyzed after topical administration into the active form. Studies done on eye tissues or plasma by radio-HPLC could not detect the prodrug in these tissues, whereas the active form was identified in cornea, aqueous humor and iris/ciliary body for at least 8 h postdose [58]. When the presence of radioactively marked tafluprost in different organs was studied, the difference of concentration between eye and systemic organs was pointed out. After 24 h, tafluprost-derived material was still detectable in the eye, whereas in systemic tissues and organs there was no accumulation. Tissue levels in the main organs of absorption and elimination were greater than plasma levels [58].

The study proved that tafluprost and its metabolites could not cross the blood–brain barrier and the placenta proved to be an effective barrier, allowing only a low dose of radioactivity to penetrate (0.1% dose/fetus). Radioactivity levels in milk tended to be greater than those in plasma, but AUC_{0-96} was similar for both fluids [58].

The similar absorption profile of radioactively marked drug in iris/ciliary body and aqueous humor indicate an accelerated exchange between the two tissues and this was postulated to be a possible enhancing mechanism of the uveoscleral outflow, which is in fact considered the main hypotensive effect of the drug [54].

In rats there was a gender difference regarding the systemic radioactivity after exposure to drug-derived materials, whereas the ocular radioactivity was comparable. This difference was postulated to be linked to a greater renal elimination in female because of a lower hepatic activity [58].

Tafluprost acid was the primary *in vivo* systemic metabolite of tafluprost, but this was rapidly superseded by its metabolite 1,2,3,4-tetranor acid. The latter was the main *in vivo* metabolite in well-perfused tissues such as liver and lung [58].

The β-oxidation degradations of the α-chain are well documented for prostaglandin analogs [59,60]. Other minor metabolites identified were phenyl ring-hydroxylated derivatives of the side-chain shortened acids. Tafluprost lacks a hydroxyl group and this would prevent extensive transformations of the ω-chain by a prostaglandin hydrogenase, thus possibly prolonging its efficacy in the eye.

5.4 Clinical efficacy

Many clinical studies on efficacy and safety of tafluprost have been carried out in different countries [63-68].

Three Phase I studies were conducted on healthy subjects. One aimed to compare safety, tolerability and pharmacodynamics of ascending doses of tafluprost (0.0001, 0.0005, 0.0025 and 0.005%) and demonstrated a good tolerability also for the highest tested concentrations [65]. The second study compared tafluprost with latanoprost, and the authors concluded that tafluprost 0.005% was more effective in reducing the IOP than latanoprost 0.005% while confirming good tolerability and safety [64]. The third study evaluated the pharmacokinetics, efficacy and safety profiles of preserved and preservative-free tafluprost 0.0015%, showing similar pharmacokinetic properties and good tolerability for both formulations [68].

Based on results from a Phase II dose-response study, the therapeutic concentration of tafluprost was set at 0.0015% [69]. A second Phase II study compared tafluprost 0.0015% with latanoprost 0.005% and results showed comparable effects on the extent, duration and stability of IOP reduction [70].

Different Phase III clinical studies on tafluprost have been conducted so far. One study was carried out with a noninferiority design, aimed at comparing the efficacy of tafluprost and latanoprost. Results confirmed the noninferiority of tafluprost, with a mean IOP reduction of 6.6 ± 2.5 mmHg (27.6 ± 9.7%) [71]. Such results were confirmed in a large multicenter study of similar design [72] that showed a substantial IOP-lowering effect for both latanoprost and tafluprost of 7.7 mmHg and 7.1 mmHg, respectively. Although the IOP-lowering effect during the study was slightly larger with latanoprost, the noninferiority of tafluprost over the diurnal IOP measurements was shown with ANOVA. Egorov and Ropo investigated the efficacy and safety of tafluprost as an adjunctive therapy to timolol in patients with open-angle glaucoma or ocular hypertension, uncontrolled by timolol monotherapy [67], demonstrating a consistently greater reduction in IOP by tafluprost if compared with vehicle. A clinical equivalence between preservative-free and preserved 0.0015% tafluprost formulations has been reported in a Phase III study by Hamacher *et al.* in open-angle glaucoma and ocular hypertensive patients [73], thus confirming previous data from Uusitalo *et al.* in healthy volunteers.

5.5 Safety and tolerability

In 2007, Sutton *et al.* first compared in a Phase I study the safety and tolerability of tafluprost and latanoprost in healthy subjects [64]. In their study they considered both systemic (palpitations, fatigue, dry throat, nasopharyngitis, dizziness, headache, abnormal liver function, syncope, epistaxis, sneezing) and ocular (foreign-body sensation, chemosis, dry eye, eye pain, eye irritation, keratitis, lacrimation, conjunctival hyperemia, optic disk disorders, photophobia, tired eyes, blurred vision) adverse events. No serious adverse events were reported and the authors concluded that systemic safety was similar for tafluprost, latanoprost and placebo. Ocular adverse effects were mild to moderate in severity and the most common side effect was ocular hyperemia. Photophobia and ocular hyperemia were more common with tafluprost 0.005 or 0.0025% compared with latanoprost 0.005%. Sutton *et al.* noticed similar findings in another Phase I study comparing the effects of ascending doses of tafluprost (0.0001, 0.0005, 0.0025 and 0.005%) [65]; the most frequently observed adverse effect was mild-to-moderate and highly concentration-dependent hyperemia. It is noteworthy that many of the doses used in these studies exceeded the currently available 0.0015% preparations.

In a recent Phase III study, Uusitalo *et al.* compared the safety of tafluprost 0.0015% and latanoprost 0.005% in patients with open-angle glaucoma or ocular hypertension over a period of 24 months. From 533 patients randomized, 402 completed the study and there were no unexpected adverse events associated with long-term tafluprost treatment. Overall, ~ 65% of the patients in each treatment group reported adverse events, which were predominantly mild to moderate in severity. Conjunctival hyperemia was reported as the most frequent side effect, with similar overall rates in the two groups and 7.4% of patients reporting ocular or conjunctival redness during the study period. Parrish *et al.* reported an incidence rate of hyperemia of 5 – 20% with latanoprost, 35 – 50% with travoprost and 35 – 50% with bimatoprost at 12 weeks [3]. This data could be particularly interesting taking into account that hyperemia seems to affect negatively patient compliance and persistency with the prostaglandin analogs [6,74].

Treatments used in the abovementioned studies contained preservatives. Similar data were obtained by Uusitalo *et al.* administering preserved and preservative-free tafluprost formulations in healthy subjects with ocular hyperemia of predominantly moderate (preserved tafluprost) or mild (preservative-free tafluprost) severity [68]. In a recent study, Uusitalo *et al.* investigated the tolerability of a preservative-free tafluprost formulation in patients exhibiting ocular-surface side effects during preserved latanoprost treatment [75]. Over a 12-month period a significant reduction in the number of patients exhibiting subjective symptoms was reported, with a consistent pattern of shift of the side effects towards a lower grade of intensity for all variables studied. Also, preservative-free tafluprost conjunctival hyperemia was significantly lower than the previous latanoprost treatment. The authors concluded

that patients with ocular-surface side effects might benefit from switching to a BAK-free prostaglandin. Hommer *et al.* obtained similar results in an observational study, demonstrating that preservative-free tafluprost can be considered a safe medication in patients with poor IOP control and/or tolerability issues with their previous antiglaucoma medication [76].

6. Conclusion

Tafluprost is the first prostaglandin analog that has been commercialized in both preserved and preservative-free formulations. Efficacy and safety of tafluprost 0.0015% ophthalmic solution were investigated in many clinical studies and results from two Phase III studies have been recently published. The existing data about tafluprost indicate good tolerability and safety and an IOP-lowering effect comparable to that of latanoprost. No data comparing tafluprost to other prostaglandin analogs are available yet. Pharmacokinetics and efficacy profiles of preserved and preservative-free tafluprost formulations have been shown to be similar. As preservative-free formulations are associated with reduced adverse reactions, tafluprost has the potential of higher patient adherence and compliance to treatment if compared with the other existing prostaglandin derivates. However, additional studies are required to define better the positioning of this new promising formulation among the antiglaucoma drugs.

7. Expert opinion

Considering all the potential side effects related to preservatives, it is reasonable to postulate that, for chronic therapies, preservative-free formulations should be preferred.

Several studies demonstrated that conjunctival alterations related to chronic antiglaucoma therapies are significantly reduced if preservative-free formulations are used [20,77-79]. Glaucoma patients are usually on topical therapies with multiple drugs for decades. The development of formulations with more compounds in the same bottle leads to a reduction in the number of instillations.

Different studies have proved that most glaucoma patients are in therapy with preserved eye drops and discomfort is strictly related to the number of instillations a day [24,25]. In the future, the use of nonpreserved eye drops is warranted, whenever they become available, to improve patients' compliance by reducing the ocular-surface side effects and improving the probability of filtering surgery success. Most physicians are likely to switch their patients to preservative-free formulations, should the latter prove to have the same IOP-lowering effect of preserved ones. More data should be obtained regarding the stability and efficacy of preservative-free formulations so that the physician is provided with complete data and the patient is reassured of the efficacy of the new formulation. In the future, fixed combinations without preservatives should also be studied, to reduce further the effect on the ocular surface, simply by reducing the number of instillations.

Within a few years most of the chronic topical therapies are going to be available in preservative-free formulations, and more fixed formulations with different active compounds will be commercialized. Nowadays, all fixed formulations include beta-blockers, with well-known contraindications, because of systemic side effects.

In the last several years compliance has gained importance, as it has proved to be related to the modality of administration of the drugs. Future goals should focus on reducing the number of drops per day, thus possibly reducing the side effects. While patients should be made ever more aware of the importance of following the prescription precisely, at the same time medications with fewer side effects and an easy administration schedule should be the first choice.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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