EXPERT OPINION

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Overview of the BAK-free travoprost/timolol BAK-free fixed combination

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Introduction: Glaucoma is the second leading cause of blindness globally, representing a significant public health concern. More than 60 million people are affected by glaucoma worldwide; as this population ages, the number is expected to increase. Glaucoma is a collection of heterogeneous diseases sharing common clinical characteristics. The goal of treatment is to prevent significant visual dysfunction through reduction of intraocular pressure (IOP).
Areas covered: This is a review of the current literature about combination therapeutic regimens for the reduction of IOP, focusing on the risk : benefit profile of a fixed-combination therapy using travoprost and timolol.
Expert opinion: Since the debut of prostaglandin analogues in the 1990s, only modest innovation has occurred in glaucoma pharmacology. A growing body of research has established that the preservative benzalkonium chloride (BAK) might not be the benign contributor expected of excipient ingredients. Thus, BAK-free treatments were developed, with the goal of IOP reduction without furthering ocular surface disease symptoms. The BAK-free travoprost/timolol combination represents an important addition to glaucoma medication options and may fill an unmet need in this therapeutic arena.

Keywords: benzalkonium chloride, fixed-combination therapy, glaucoma, timolol, travaprost

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1. The global burden of glaucoma

Glaucoma is the second leading cause of blindness in the world and represents a significant public health concern. An estimated 2.2 million people are affected with open-angle glaucoma in the United States [1] and 60.5 million people are affected by open-angle and angle-closure glaucoma worldwide [2]. As the global population ages, these numbers are expected to rise to more than 3 million [1] and 79.6 million [2], respectively, by 2020.

2. Glaucoma clinical characteristics

Glaucoma is a collection of heterogeneous diseases sharing common clinical characteristics. Classically, glaucoma has been described as a condition in which elevated intraocular pressure (IOP) damages the optic nerve, resulting in peripheral visual field loss. This description generally holds true for secondary glaucomas arising from underlying ocular or systemic conditions that raise IOP; these secondary glaucomas collectively represent a minority of all cases, although the proportion varies by geographical region. More recently, the relationship between glaucoma and elevated IOP has been challenged by the observation in epidemiologic studies that elevated IOP is neither necessary nor sufficient on its own to cause glaucoma [3]. Many individuals have elevated IOP but no glaucoma, a state referred to as 'ocular hypertension'. Other patients have classic glaucomatous optic nerve and visual field changes in the absence of elevated IOP, a condition referred to as 'low-tension (or more accurately,

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Box 1. Drug summary.

Drug name	DuoTrav APS ophthalmic solution (travoprost 0.004%/timolol 0.5% fixed combination)
Phase	Launched
Indication	Glaucoma or ocular hypertension
Pharmacology description	Prostaglandin F2 alpha receptor agonist Beta 1 adrenoreceptor antagonist Beta 2 adrenoreceptor antagonist Beta adrenoreceptor antagonist Muscarinic receptor agonist Prostaglandin FP receptor agonist
Route of administration	Topical ocular
Chemical formula	$C_{39}H_{59}F_3N_4O_9S$
Pivotal trial(s)	[60]

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normal-tension) glaucoma'. Both normal-tension glaucoma and high-tension glaucoma can be considered a single entity, termed 'primary open-angle glaucoma', which exists across the range of IOP values.

Primary open-angle glaucoma (POAG) is by far the most common form of glaucoma; its pathophysiology is poorly understood. The condition is characterized by loss of retinal ganglion cells and their axons, which comprise the optic nerve, resulting in characteristic optic nerve atrophy and progressive loss of peripheral vision. Elevated IOP is not considered a feature of POAG but is a risk factor for both its development and progression. In addition to elevated IOP, other risk factors for glaucoma have been elucidated from major clinical trials and include increased age [4-7], lower central corneal thickness [4-7], ethnicity (those of African–American [8], Hispanic [9] and Asian–American [10] descent are at higher risk than Caucasians), hemorrhage of the optic nerve [11], lower systolic [6] and diastolic [12] perfusion pressure, and exfoliation syndrome [6].

3. The therapeutic paradigm in glaucoma

The goal of glaucoma therapy is to prevent significant visual dysfunction and the single therapeutic option for glaucoma management available today is the reduction of IOP. Lowering IOP prevents or delays the development of POAG in hypertensive eyes [13,14] and reduces the risk of progression in established POAG with either elevated [15] or normal IOP [16,17]. IOP is defined as the balance between aqueous fluid production and the rate of its egress from the eye's outflow pathways. Therapies to lower IOP either reduce aqueous synthesis or enhance aqueous outflow. IOP reduction can be achieved through the use of topical or oral medications [18], laser therapy [18] or incisional surgeries [18] that essentially bypass dysfunctional outflow pathways and create alternative outflow channels for aqueous fluid. A dose–response relationship between IOP reduction and reduced risk of progression has not been established and the optimal magnitude of IOP reduction needed to confer protection has not been elucidated. Expert consensus suggests a 25 – 35% initial reduction for early or moderate glaucoma, 40 – 50% reduction for advanced glaucoma and successive reductions if progression is noted over time [18,19]. A challenge in glaucoma management is striking the balance between the risks of disease progression and the risks of IOP-lowering therapies.

Therapy is generally applied in a stepped algorithm to achieve the desired IOP reduction, beginning with topical medical therapy, progressing to laser therapy and ultimately including surgery for recalcitrant cases. Medicated eye drops are the least invasive treatment and are easily discontinued if not well tolerated. Ideally, a regimen of monotherapy is preferred because of its simplicity and safety relative to more complex regimens [18,19]. A substantial proportion of patients (up to 40%) will not achieve even a modest 20% IOP reduction with monotherapy; these patients may require a combination of two or more medications to reach IOP goals [14]. Given the large number of glaucoma patients who require multidrug regimens, several commonly paired medications are available formulated in fixed combinations.

4. Fixed-combination glaucoma formulations in clinical practice

There are numerous advantages, and relatively few disadvantages, to the use of fixed-combination therapy for the management of glaucoma [20-23]. The primary disadvantage to the use of these combinations is the inability to titrate individual component doses. For instance, the fixed combination of dorzolamide 2%/timolol 0.5% is approved for twice-daily dosing, whereas timolol monotherapy can be dosed once or twice daily and dorzolamide monotherapy is labeled for three-times-daily dosing. Additionally, a constituent might be available in different strengths (e.g., timolol in 0.25 or 0.5% formulations) but fixed combinations with timolol uniformly incorporate the 0.5% strength. This dose may be more than some patients need for an optimal balance between IOP control and safety.

With these minor disadvantages in mind, there are many important advantages to fixed-combination therapy. Patients requiring two medications for adequate IOP control can enjoy regimen simplicity with the use of a fixed-combination product. Because early-stage and moderate glaucoma are asymptomatic and treatment does not ameliorate any symptoms, there is no positive feedback to encourage adherence to glaucoma therapy, which is notoriously poor [23]. Regimen complexity is among the barriers to adherence with glaucoma therapy [24]. Thus, it is reasonable to assume that the simplicity offered by fixed-combination therapy, with two medications instilled with fewer doses of drops per day from fewer bottles, should improve therapeutic adherence.

Article highlights.

- Glaucoma is the second leading cause of blindness in the world and represents a significant public health concern.
- Reduction of intraocular pressure (IOP) is the primary therapeutic option for glaucoma management today, but reaching a balance between the risk of disease progression and the risk of IOP-lowering therapy is difficult.
- Use of fixed-combination products to lower IOP is advantageous from the standpoint of patient compliance, but some combinations contain buffers, preservatives and other inactive ingredients that have been linked to ocular surface cell dysfunction.
- In particular, benzalkonium chloride has been found to be harmful to the corneal and conjunctival epithelial cells and goblet cells. Reducing exposure to benzalkonium chloride has been found to improve ocular surface disease symptoms while not affecting the efficacy of topical treatments for IOP reduction.
- Travoprost/timolol fixed-combination treatment without benzalkonium chloride has been found to be effective in achieving IOP control while offering protection to those patients who have relative or absolute contraindications to exposure to this compound.

This box summarizes key points contained in the article.

Another benefit of fixed-combination therapy is avoidance of the washout effect, which occurs when patients instill multiple medications in rapid succession and wash out the first administered medication with the second medication before the first has been adequately absorbed. Administering two medications simultaneously in the same solution ensures adequate residence time on the ocular surface for optimal absorption.

In the US, patients with adequate insurance coverage for prescription medications may save one co-payment per refill with a fixed-combination drug versus the two individual products.

A bottle of eye drop medication contains more than just the active ingredients, however. Each dose contains a liquid vehicle, buffers, preservatives and other inactive ingredients that enhance the stability, solubility and sterility of the product. Of these excipients, chronic exposure to preservatives, specifically benzalkonium chloride (BAK), has been linked to dysfunction of ocular surface cells [25,26]. Fixed combinations minimize exposure to these excipient ingredients by reducing the number of drops required per day to dose multiple medications.

5. The rationale for a BAK-free fixed-combination glaucoma product

Benzalkonium chloride (BAK) is ubiquitous in topical glaucoma products and is also found in many other topical ophthalmic formulations [27]. This compound is a member of the quaternium ammonium family of molecules and is a highly effective antimicrobial and antifungal agent and preservative [26]. In addition to these functions, BAK is also known to enhance ocular penetration of topically applied ophthalmic medications [28].

Unfortunately, BAK also has undesirable properties [29]. A multitude of studies spanning several decades has documented that BAK is deleterious to the health of ocular surface cells, including corneal and conjunctival epithelial cells and goblet cells. In cultured human cell lines, BAK has been shown to diminish the viability of corneal [25,26] and conjunctival epithelial cells [25,30,31], as well as the trabecular meshwork and nonpigmented ciliary epithelial cells *in vitro* [30]. The clinical consequences of acute and chronic BAK exposure to the ocular surface include subclinical conjunctival and subconjunctival inflammation [31-33], impairment of the corneal epithelium's barrier function [32-36], loss of goblet cells [37], tear film destabilization [34,36], subjective patient complaints of dryness and irritation [38,39], punctate keratitis [39] and reduction in the success rate for glaucoma filtration surgery [32,40-42]. BAK has also been linked to cataract formation [43].

The negative impact of BAK on the ocular surface becomes more important in light of the high prevalence of ocular surface disease among patients with glaucoma. Two recent studies reported the prevalence of the symptoms of ocular surface disease among glaucoma patients to be in the range of 48 – 59% [44,45] when using the Ocular Surface Disease Index (OSDI), a validated instrument for assessing ocular surface disease symptomatology. The survey of the literature by Stewart *et al.* estimated the prevalence of ocular surface disease among patients with suspected or established glaucoma at 42%, with 36% of these cases considered severe ocular surface disease [46]. Among patients with comorbid glaucoma and ocular surface disease, quality of life measured with the validated 15-item Glaucoma Quality of Life instrument [47] correlated with surface symptoms assessed with the OSDI [48]. Importantly, reducing exposure to BAK was found to improve the symptoms of ocular surface disease [49].

Patients with both glaucoma and ocular surface disease who were treated with the prostaglandin latanoprost preserved with BAK were randomized in double-masked fashion to continue the same therapy or transition to a BAK-free formulation of the prostaglandin, travoprost. Twelve weeks after randomization, mean OSDI scores were lower in the group using BAK-free travoprost than latanoprost with BAK, and more subjects in the BAK-free travoprost group had achieved normal OSDI scores than in the latanoprost with BAK group.

Therefore, a BAK-free fixed combination of glaucoma medications would fill a significant unmet need because most of the currently available therapeutic options are preserved with BAK. Many glaucoma patients need more than one medication for IOP control, and fixed combinations offer numerous advantages over concomitant therapy with individual products.

6. The BAK-free formulation of the travoprost/timolol fixed combination

Travoprost 0.004% is a prostaglandin analogue that lowers IOP by increasing aqueous outflow through the uveoscleral outflow pathway. Timolol maleate 0.5% is a beta-blocker that lowers IOP by reducing aqueous production by the ciliary epithelium. The rationale for combining these two drugs in a fixed combination has already been discussed [50]. Briefly, these drugs have complementary mechanisms of action, share similar pharmacokinetics for ease of dosing and exhibit physicochemical properties that make them compatible for co-formulation (**Box 1**). The first fixed combination formulation of travoprost/timolol was preserved with BAK and entered the global marketplace in 2006 [50].

A new formulation of travoprost/timolol fixed combination is preserved with polyquaternium-1 rather than BAK. The polyquaternium family of molecules has a central quaternary ammonium (NR4+ with R being an alkyl or aryl group) in common. They are used in disinfectants, fabric softeners and also have antimicrobial activity [51]. The polyquaternium family members have substantial structural diversity and are named by number in the order that they are discovered or synthesized. Polyquaternium-1 (ethanol, 2,2′,2″-nitrilotris-, polymer with 1,4-dichloro-2-butene and N,N,N′,N′-tetramethyl-2-butene-1,4-diamine) is a polycationic polymer that is commonly used as a preservative in contact lens solutions and has also been used in a formulation of brimonidine for glaucoma management [52]. It is structurally derived from BAK but differs from it in important ways, the most important of which being that polyquaternium-1 is attracted by bacterial cell walls but repelled by human corneal epithelial cells [53], which may underlie its relatively more favorable ocular safety profile in comparison to BAK.

7. The efficacy and safety of BAK-free travoprost/timolol

The clinical efficacy and safety of the travoprost/timolol fixed combination preserved with BAK has been established [54-59]. Given that one function of BAK is to enhance the penetration of co-administered molecules, concern arises that removing BAK from the formulation might reduce ocular penetration of the active drugs and thus reduce clinical efficacy of these formulations. To address this concern, Kitazawa *et al.* conducted a prospective, randomized, double-blind comparison of the safety and efficacy of travoprost 0.004%/timolol 0.5% preserved with BAK to travoprost 0.004%/timolol 0.5% BAK-free [60]. In this noninferiority trial, 388 subjects with ocular hypertension or POAG were treated with one of the two formulations for 6 weeks. IOP was measured on two pre-randomization baseline visits and at 2 and 6 weeks after randomization, with pressure assessed at 9 a.m., 11 a.m. and 4 p.m. on every study visit. The outcome for declaring noninferiority was mean IOP pooled across visits and timepoints during treatment; noninferiority was declared if the 95% confidence intervals (CI) on the difference in mean IOP between groups fell within ± 1.5 mmHg. The mean IOP reduction, pooled across all visits and timepoints, was 8.0 mmHg in the travoprost/timolol BAK-free group and 8.4 mmHg in the travoprost/timolol with BAK group (p = 0.09). The IOP outcomes at each timepoint in this study are shown in **Figure 1**. The mean pooled difference between groups was 0.4 mmHg (95% CI –0.1 to 0.8), demonstrating noninferiority of the BAK-free formulation to the BAK formulation. The most common drug-related ocular adverse event was ocular and conjunctival hyperemia, occurring in 11.8% of the BAK-free group and 13.0% of the BAK-containing group.

The finding by Kitazawa *et al.* [60] that removing BAK from the formulation had no effect on IOP-lowering efficacy of the product is consistent with other studies. Head-to-head comparisons of the efficacy and safety of travoprost with BAK versus travoprost formulated with the proprietary SofZia™ preservative system (Alcon, Fort Worth, TX) [61,62], travoprost with BAK versus travoprost with polyquaternium-1 [63], brimonidine with BAK versus brimonidine with the proprietary Purite™ preservative system (Allergan, Inc., Irvine, CA) [64], dorzolamide 2%/timolol 0.5% with BAK versus preservative-free dorzolamide 2%/timolol 0.5% [65] and timolol with BAK versus timolol with reduced [66] or no BAK [67] all demonstrated that removal of BAK from the formulation had no meaningful effect on IOP-lowering efficacy. Further evidence that BAK is not important for IOP reduction comes from the observation that the efficacy of travoprost/timolol BAK-free in the study by Kitazawa *et al.* [60] was comparable in magnitude to the efficacy of travoprost/timolol with BAK reported by other investigators [54-59]. Taken together, these observations suggest that the efficacy results of studies of BAK-containing formulations of IOP-lowering medications can be generalized to results with BAK-free formulations.

8. BAK-free Travoprost/timolol may be less toxic to the ocular surface

By virtue of not containing BAK, travoprost/timolol preserved with polyquaternium-1 may be less toxic to the ocular surface. In an in-vivo rat model that included both clinical and corneal confocal microscopy assessments after 11 days of twice-daily dosing with various concentrations of BAK, polyquaternium-1 and balanced salt solution, polyquaternium-1 – even at high doses – was significantly less toxic to the corneal and conjunctival surface than BAK [68].

The acute ocular surface effects of BAK-free travoprost/timolol versus travoprost/timolol with BAK were evaluated in a rabbit model *in vivo* that also included animals treated with phosphate-buffered solution and latanoprost/timolol with BAK [69]. Each drug was dosed 15 times at 5-min intervals, and assessments were performed at 4 h and 1 day after dosing, using slit lamp inspection, confocal microscopy, conjunctival impression cytology and immunohistochemistry. Significantly less surface toxicity by all methods of assessment was seen

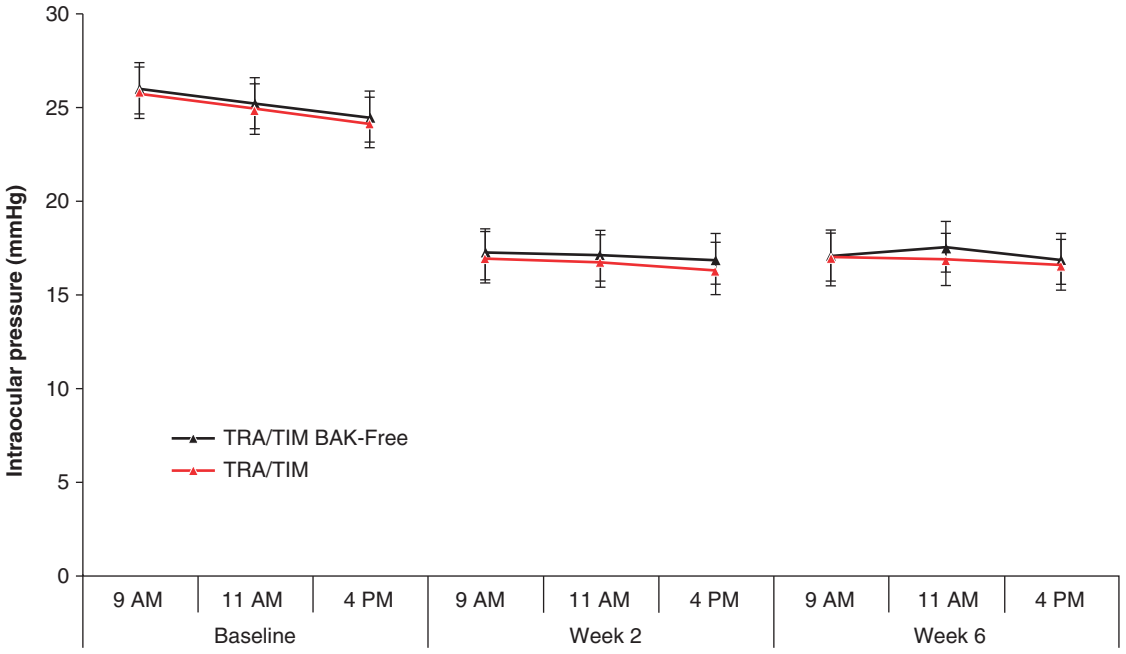

Figure 1. Intraocular pressure (IOP) at each timepoint in the comparison of travoprost/timolol BAK-free and travoprost/timolol with BAK [58].

with BAK-free travoprost/timolol versus the two BAK-containing treatments.

In cultured human conjunctival cells, BAK-free travoprost/timolol was associated with significantly less oxidative stress and lower rates of apoptosis than travoprost/timolol with BAK or latanoprost/timolol with BAK [70]. In cultured human corneal, conjunctival and trabecular meshwork cells, BAK-free travoprost/timolol was associated with greater cell viability in live-dead assays than either travoprost/timolol with BAK or latanoprost/timolol with BAK [71,72].

9. Clinical summary of BAK-free travoprost/timolol

The fixed combination of travoprost/timolol preserved with polyquaternium-1 lowers IOP substantially with minimal safety and tolerability issues. Importantly, this product provides the benefits of fixed combination therapy without BAK exposure to patients on multidrug regimens. In animal models and in-vitro studies with human ocular surface cell lines, travoprost/timolol BAK-free was significantly less toxic than glaucoma products preserved with BAK. The travoprost/timolol BAK-free combination therapy satisfies an unmet need in glaucoma therapy.

10. Expert opinion

The development of timolol maleate for IOP reduction in 1977 [73] launched a paradigm shift in the management of glaucoma and heralded the dawn of the modern era of glaucoma pharmacology. Virtually overnight, timolol supplanted pilocarpine as the preferred first-line therapy for glaucoma. In the mid-1990s, our armamentarium of glaucoma medications expanded, with the introduction of three new drug classes: topical carbonic anhydrase inhibitors, alpha-adrenergic agonists and prostaglandin analogues, the last of which brought forth a major shift when they replaced timolol as the preferred first-line therapy. At the peak of this period of rapid drug development, when clinicians had more drug choices than ever before with which to individualize glaucoma regimens, it was estimated that physicians could choose from over 56,000 different possible multidrug regimens [74].

Since the introduction of the prostaglandin analogue class in the mid-1990s, there has been little innovation in glaucoma pharmacology. As we now consider the unmet needs in glaucoma therapy and look forward to a new wave of drug discovery (with possible introduction of rho kinase inhibitors and other novel drug classes), there is value in enumerating the preferred attributes of an ideal IOP-lowering medication.

First and foremost, an ideal drug would be extraordinarily safe and well tolerated. Given that glaucoma is not life threatening and that glaucoma therapy is, in essence, prophylactic – as we are preventing further damage but not reversing existing damage – the threshold for side effects is quite low. One of the reasons that prostaglandins replaced beta-blockers as first-line therapy is their relative safety profiles. Whereas there are contraindications to beta-blockers, as administration to patients with pulmonary or cardiac disease can in rare cases be associated with significant morbidity and mortality, there are no absolute contraindications

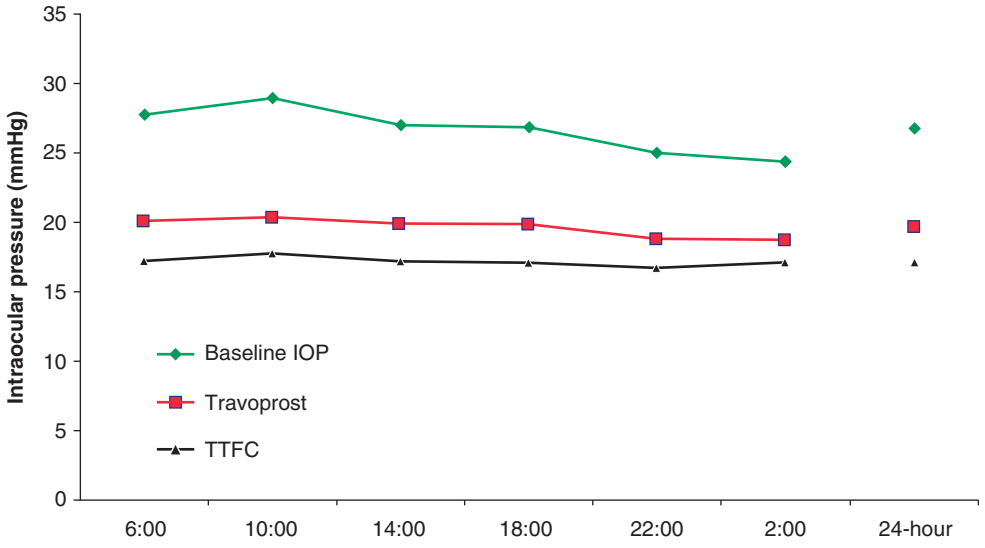

Figure 2. Intraocular pressure (IOP) at each time point and pooled over 24 h in the comparison of travoprost.timolol with BAK and travoprost [52].

to prostaglandin therapy. The established side effects of prostaglandin therapy, including ocular hyperemia, eyelash growth and hyperpigmentation of the lids and iris, are cosmetic rather than safety issues. Travoprost/timolol BAK-free is extremely well tolerated by patients and its safety profile is largely characterized by these cosmetic issues (predominantly hyperemia). Serious beta-blocker side effects are exceedingly rare because we have learned over time to avoid prescribing products containing beta-blockers to at-risk individuals in clinical practice.

When we think of drug safety, we focus most often on the safety of the active ingredients in a formulation. In recent years, a growing body of research has clearly established that the ubiquitous preservative BAK might not be the 'innocent bystander' we require excipient ingredients to be. BAK has significant and clinically important deleterious effects on the ocular surface cell population, including corneal and conjunctival epithelial cells and goblet cells, which are ocular surface mucin-producing cells that play a key role in tear film stability. Studies have clearly demonstrated that glaucoma patients have a high prevalence of ocular surface disease symptoms [44,45] and that reducing exposure to BAK improves these symptoms [49]. In this light, there has been a movement in recent years to develop IOP-lowering drugs in BAK-free formulations. Travoprost, timolol and brimonidine are all available in BAK-free formulations. These three drugs represent three distinct drug classes and thus facilitate BAK-free management of patients on multidrug regimens. Fixed drug combinations have numerous advantages over concomitantly dosed constituents. To date, the only fixed combination treatment without preservative available for the treatment of glaucoma is dorzolamide/timolol. The BAK-free travoprost/timolol combination represents an important addition to the global marketplace of glaucoma medications and fills an unmet need in this therapeutic arena.

The simpler the regimen, the more likely patients are to adhere to it. An ideal glaucoma drug would have favorable pharmacokinetics that allow once-daily dosing. A once-daily fixed combination would have the added advantage of delivering a full day's dose of two medications in a single drop, as does BAK-free travoprost/timolol. Several studies have demonstrated that the effect of travoprost on IOP endures beyond 24 h post-dose, whether or not the formulation is preserved with BAK [61]. Based on a clinical study of travoprost/timolol with BAK, evening dosing provides superior IOP reduction to morning dosing [75].

Intraocular pressure fluctuation has emerged in some [76-79], but not all [80], studies as a potential risk factor for glaucoma progression, bringing greater attention to the 24-h IOP-lowering profiles of some glaucoma treatment products. Recent studies have demonstrated that supine IOP is highest at night when measured both in healthy subjects [81] and glaucoma patients [82]. Therefore, an ideal glaucoma medication offers consistent IOP reduction over 24 h. To date, no 24-h studies have been conducted with travoprost/timolol BAK-free, but three 24-h studies have been conducted with travoprost/timolol with BAK [54,55,75]. Based on the noninferior IOP lowering of these two formulations, the results are thought to be generalizable to the travoprost/timolol BAK-free formulation [60]. In these studies, the travoprost/timolol combination product lowered IOP significantly at all time points throughout a 24-h period [54,55,75], produced a significantly lower mean 24-h IOP (-2.4 mm Hg) compared with travoprost monotherapy (**Figure 2**) [54] and lowered IOP more effectively than did the latanoprost/timolol fixed combination in patients with exfoliation glaucoma (**Figure 3**) [55].

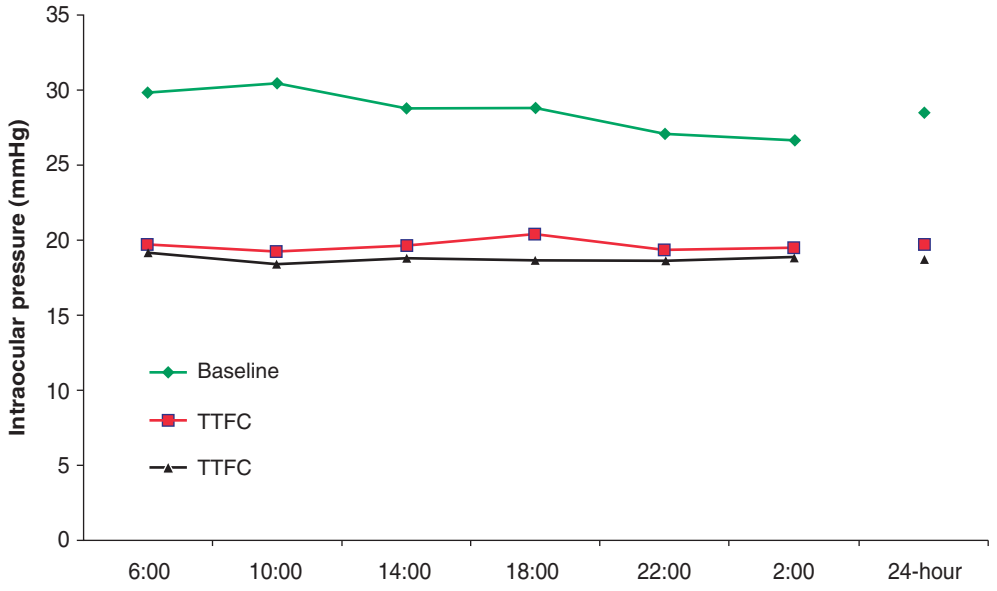

Figure 3. Intraocular pressure (IOP) at each time point and pooled over 24 h in the comparison of travoprost/timolol with BAK and latanoprost/timolol [53].

In summary, it is worthwhile considering where travoprost/timolol BAK-free fits into a stepped therapeutic regimen. In the strictest sense, the product is ideal for patients who require multiple medications to achieve IOP control and who have relative (e.g., ocular surface disease) or absolute (e.g., BAK allergy) contraindications to BAK exposure. In a broader sense, and in light of the preponderance of data supporting the detrimental effects of BAK on the ocular surface and the potential reduction of filtering surgery success after chronic BAK exposure, perhaps the time has come to ask whether minimizing BAK exposure should be a therapeutic goal for all glaucoma patients, even those who have not manifested BAK intolerance.

Declaration of interest

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