



REVIEW

A Narrative Review of Ocular Surface Disease Related to Anti-Glaucomatous Medications

Xiaoyu Zhou · Xinyue Zhang · Dengming Zhou · Yang zhao ·

Xuanchu Duan

Received: July 1, 2022 / Accepted: July 29, 2022 / Published online: August 9, 2022
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ABSTRACT

Topical anti-glaucomatous medications are still the most important measure to lower intraocular pressure. Large number of studies have confirmed that long-term use of anti-glaucomatous eye drops, especially containing benzalkonium chloride, a preservative, can cause or aggravate ocular surface injury. Ocular surface diseases damage the ocular microenvironmental health status, reduce the patients' compliance with the treatment, and finally affect the treatment result. Therefore, the ocular surface management of patients with glaucoma is very important. This includes the selection of drugs that are better tolerated according to individual conditions, preservative-free formulations, drugs that protect against ocular surface disease, or selecting surgery and laser treatment, to prevent the damage to the ocular surface by topical anti-glaucomatous drugs.

Keywords: Anti-glaucomatous medications; Benzalkonium chloride; Ocular surface disease; Preservative-free formulation

Key Summary Points

This review aims to update and summarize the causes and management of ocular surface disease induced by anti-glaucomatous medications in relation to patients' eye health and drug compliance. The preservative, especially benzalkonium chloride, and active pharmaceutical ingredients in these medications are the main causes of ocular surface disease.

It is recommended to use a new preservative with less toxicity or preservative-free preparations and a fixed combination formulation to reduce the incidence of ocular surface disease. Artificial tears, diquafosol sodium, and serum preparations are required to alleviate symptoms. Surgical treatment is also an option if necessary.

X. Zhou · X. Zhang · Y. zhao · X. Duan (✉)
Changsha Aier Eye Hospital, Changsha, Hunan Province, China
e-mail: duanxchu@csu.edu.cn

X. Zhou · X. Zhang · D. Zhou · Y. zhao
The Second Xiangya Hospital, Central South University, Changsha, Hunan Province, China

X. Duan
Aier School of Ophthalmology, Central South University, Changsha, Hunan Province, China

INTRODUCTION

As the global population ages, glaucoma has become the second leading cause of blindness, and is expected to affect 112 million individuals worldwide by 2040 [1]. Glaucoma is a heterogeneous group of neurodegenerative ocular diseases characterized by progressive visual field loss and optic nerve atrophy. The pathological increase of intraocular pressure (IOP) caused by the imbalance of aqueous humor production and drainage is the main risk factor for irreversible optic nerve injury in glaucoma. Currently, topical anti-glaucomatous medications continue to be the mainstay of therapy for controlling IOP. However, most patients with glaucoma require long-term or lifelong use of eye drops, which is associated with ocular surface diseases (OSD) including dry eye, meibomian gland dysfunction, and ocular chronic allergy [2].

OSD is a multifactorial disorder of internal environment balance between tear film and ocular surface morphological and functional units, resulting in abnormal tear quality, quantity, or dynamics, accompanied by ocular surface inflammation, tear film instability, visual disturbance, and ocular discomfort [2]. The pathological changes of OSD are closely related to dysregulation of cellular phenotypes, such as the decrease of goblet cell density, inflammatory cell infiltration, reduced corneal sensitivity, and corneal nerve fiber loss [3]. The estimated incidence of OSD in patients with glaucoma varies from 38.5% to 60%, which is much higher than that of the general population. Moreover, 49–59% of patients using topical anti-glaucomatous medications suffer OSD, while the prevalence of OSD in normal populations over 50 years old ranged from 5% to 30% [2, 4]. The long-term use of topical anti-glaucomatous medications, especially those containing preservatives, is the main factor leading to induction or aggravation of OSD.

Topical monotherapy is currently the preferred treatment for IOP control in accordance with European Glaucoma Society Terminology and Guidelines for Glaucoma [5]. However, up to approximately 50–75% of patients require

multidrug combination therapy to achieve the target IOP. The increased use of drug types and frequency may lead to poor ocular surface health for patients with glaucoma [6, 7]. The development of OSD has a significant adverse impact on the patients' drug compliance, treatment satisfaction, quality of life, and also affects the treatment results [8]. Furthermore, OSD is associated with a higher anti-glaucomatous surgical failure rate. Therefore, the management of OSD in patients with glaucoma has significant clinical implications for improving the success rate of glaucoma treatment and patients' quality of life. Here we present a comprehensive review of occurrence and management of OSD related to pharmaceutically active ingredients and preservatives of anti-glaucomatous medications.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DAMAGE TO OCULAR SURFACE BY ACTIVE INGREDIENTS IN ANTI-GLAUCOMATOUS MEDICATIONS

Currently, there are six main kinds of topical drugs commonly used for clinical treatment of glaucoma, namely β -adrenergic blockers, prostaglandin analogues (PGAs), α -adrenergic agonists, carbonic anhydrase inhibitors (CAIs), cholinergic agonists, and Rho kinase inhibitors. A number of studies have shown that these compounds can reduce the viability of corneal epithelial cells at clinically relevant concentration, but will not destroy the stability of the cell membrane [9–11]. The long-term treatment cycle of glaucoma and combination with other drugs make the risk of OSD increase substantially. On the basis of a previous review of the adverse effects of all these active pharmaceutical ingredients [12], here we update and summarize OSD induced by anti-glaucomatous medications.

Effects of β -Adrenergic Blockers on Ocular Surface

β -Adrenergic blockers can reduce the production of aqueous humor by blocking the sympathetic nerve endings of the ciliary body. Currently, the first choice of β -adrenergic blocker is mainly levobunolol (0.5%) or timolol (0.5%) available alone or in combination with other drugs for IOP reduction. However, clinically, topical application of β -adrenergic blockers was proved to have adverse effects on tear film, cornea, and conjunctiva. Symptoms of OSD include ocular aching, burning, tingling, redness, photophobia, and foreign body sensation. This leads to 2–10% of patients discontinuing medication [13]. A prospective study showed that compared with other types of anti-glaucomatous medications, β -adrenergic blockers display more serious adverse effects on the ocular surface [14].

Effects of β -Adrenergic Blockers on Tear Film

Topical use of β -adrenergic blockers can affect tear production, stabilization, and exchange. In a study which compares the effects of levobunolol and timolol on tear volume, precorneal tear film stability, and corneal epithelial barrier function in normal eyes, timolol significantly shortened the precorneal tear film breakup time (TBUT) compared to levobunolol, and both of them reduced ocular surface tear volume, which was strongly associated with dry eye symptoms [15]. In a study investigating corneal epithelial lesions in 193 eyes of 110 patients with glaucoma, tear film lipid layer, tear volume, and tear film stability were assessed; superficial punctate keratitis occurred significantly more frequently in patients using timolol (46.2%) than in those using carteolol (4.2%) but was less severe than with carteolol [16]. A cross-sectional study showed that preservative-free (PF) timolol still resulted in increased tear instability and altered corneal microstructure, suggesting that its active ingredient may also cause ocular surface damage [17].

Effects of β -Adrenergic Blocker on Cornea

Several studies have proved the corneal toxicity of β -adrenergic blockers. Timolol specifically causes extensive epithelium abscission, promotes plasma membrane pore formation and rupture [18]. Studies researching the toxicity of anti-glaucomatous medications on human corneal epithelial line cells found that β -adrenergic blockers appear to possess inhibitory and cytotoxic effects on corneal cells, and restrain the corneal epithelial barrier function [11, 19]. Another study has pointed out that a thinner corneal epithelial thickness was significantly associated with topical application of β -adrenergic blockers [20]. Mastropasqua et al. used laser scanning confocal microscopy and impression cytology to investigate the morphologic changes of the corneoscleral limbus in patients with glaucoma. They discovered that β -adrenergic blockers exhibited a worse limbal transition epithelium regularity, which means β -adrenergic blockers may delay corneal regeneration by interfering with the limbal stem cell microenvironment [21]. Furthermore, Yuan et al. established a corneal wound healing mouse model and identified the β 2AR-EGFR-ERK1/2 axis as the main mechanism of β -adrenergic blocker-induced impaired corneal epithelial regeneration [22]. A cross-sectional study of 300 eyes in 187 patients with glaucoma showed that corneal epithelial erosion occurs more in β -adrenergic blocker-instilled eyes, whereas there is no difference in ocular toxicity between CAIs and PGAs [23]. Van Buskirk also found that a portion of patients suffered superficial punctate keratitis after topical timolol maleate treatment [24]. The corneal sensitivity of elderly patients with long-term use of timolol maleate is significantly reduced. Therefore, it is recommended to regularly measure the corneal sensitivity of elderly patients with long-term topical use of timolol or betaxolol [25].

Effects of β -Adrenergic Blockers on Conjunctiva

β -Adrenergic blockers also inflict damage on the conjunctiva. An in vivo confocal microscopy and impression cytology analysis revealed that unpreserved levobunolol induced a 17%

decrease of goblet cell density compared to baseline [26]. Two animal studies using rabbits found that compared with PGAs, timolol significantly increased subepithelial collagen density and extracellular matrix (ECM), which may result in failure of filtering surgery [27, 28]. With topical use of timolol, there is a decrease in secretory epithelial cells, and vacuolation and expansion of the intracellular rough endoplasmic reticulum [29]. This may amplify the cytotoxic effect of preservatives. And a clinical study using biopsy specimens has also proved the enhanced diffuse immune response in patients with long-term use of timolol [30]. Allergic reactions due to timolol have also been reported [31].

Effects of β -Adrenergic Blockers on Lacrimal Punctum and Canaliculus

Previous studies have reported lacrimal drainage system obstruction associated with topical use of β -adrenergic blocker-containing preparations in patients with glaucoma. A cross-sectional controlled study found that timolol + dorzolamide and timolol + dorzolamide + pilocarpine had a significant association with lacrimal punctum and canaliculus obstruction [32, 33]. This study indicated that combination therapy might cause more adverse effects on the lacrimal drainage system. These two preparations both contain timolol and dorzolamide. Timolol-induced unilateral stenosis or obstruction has been reported widely [34], whereas the related adverse effects of dorzolamide have not been reported yet. A significantly higher percentage of patients with primary open-angle glaucoma (POAG) in the lacrimal drainage obstruction group (69%) were treated with timolol, compared with patients in the control group (18%) [35]. It is presumed that chronic use of β -adrenergic blockers caused lacrimal drainage system cicatricial reaction and autonomic nervous system effects [34, 36]. However, punctal occlusion has been proved to lower IOP of patients treated with topical medications for glaucoma [37]. Further studies are required to figure out the exact effects of anti-glaucomatous medications on the lacrimal punctum and canaliculus.

Effects of Prostaglandin Analogues on Ocular Surface

PGAs may act to lower IOP by promoting relaxation of the ciliary muscle and remodeling of the ECM of the ciliary myocytes. However, with the widespread clinical use of these drugs, they have been found to affect the ocular surface, including conjunctival congestion, corneal damage, and reduced central corneal thickness (CCT) [38].

Effects of PGAs on Cornea

PGAs also have adverse effects on the cornea. Recurrence of herpes simplex keratitis associated with the use of PGAs has been reported in several cases. In addition, corneal punctate epithelial erosions and dendritic keratitis are associated with the topical use of PGAs [39]. Kahook and Ammar determined the toxicity of four kinds of PGAs on human corneal epithelial cells in vitro, and found that tafluprost 0.005% with 0.010% benzalkonium chloride (BAK) and latanoprost 0.005% with 0.020% BAK exhibited the highest toxicity, followed by travoprost 0.004% with 0.015% BAK and then travoprost 0.004% with sofZia [40]. Whether the preservative has greater adverse effects on the cornea is to be proven by further experiments. Shen et al. further studied the toxicity of latanoprost on corneal stroma, and its underlying mechanisms may be associated with death receptor-mediated mitochondria-dependent apoptosis [41].

Effects of PGAs on Conjunctiva

Hyperemia is the most common side effect of PGAs, occurring in up to 65% of patients, with a higher incidence than timolol [42]. The reason may be related to nitric oxide-mediated vasodilation of the conjunctiva. Although several studies have reported decreased goblet cell density, conjunctival epithelial defects, poor Schirmer test, and decreased TBUT results after topical PGAs use [43], the effect of preservatives cannot be ruled out in this case. Biopsy specimens from human and animal studies all showed that PGAs can affect conjunctival fibroblasts; matrix metalloproteinase family

expression is upregulated in the PGAs group compared to controls, and these genes are associated with the repair of conjunctival tissue [44, 45]. An in vitro study also demonstrated that latanoprost and travoprost may protect against toxicity of BAK on conjunctiva-derived epithelial cells [46]. And a study reported a higher goblet cell count in the superior central conjunctiva after 6-month treatment with BAK-containing latanoprost compared with that in patients treated with PF timolol and BAK-containing timolol [14]. PGAs seems to harm to goblet cell less than other kinds of anti-glaucomatous medications do.

Effects of PGAs on CCT

In addition, several studies have pointed to a decrease in CCT after topical treatment with PGAs in patients with glaucoma. The reason for this may be related to the action of PGAs in degrading collagen through upregulation of matrix metalloproteinases. Considering the cornea mainly composed of collagen fibers, it is believed that topical use of PGAs causes changes in corneal biomechanical properties. A retrospective analysis showed that after 3 years of topical PGA monotherapy, patients with glaucoma had a mean reduction in CCT of 17.75 μm [47]. Other studies have also demonstrated similar results: 5 years use of latanoprost caused reduction of CCT in patients with normal-tension glaucoma [48]. CCT is considered as an independent risk factor for glaucoma progression, and it also has a significant impact on the outcome of IOP measurements [49]. Thus, with the progression of CCT thinning, the lifetime use of PGAs may increase the likelihood of overestimating the IOP-lowering effect. However, it has also been noted that IOP reduction and responder rates measured with Goldmann applanation tonometry were lower than those measured with modified surface Goldmann prism in patients with topically applied latanoprost, and no difference in IOP lowering was detected in patients with timolol [50]. This may be related to factors such as CCT changes and corneal hysteresis caused by PGAs. Therefore, it is important to measure CCT values continuously during the follow-up of glaucoma, especially in patients treated with PGAs. More

follow-up studies are also required to show the PGAs-induced alterations of corneal biomechanics and their relationship to IOP measurements.

Although some basic research has demonstrated the toxicity of PGAs to corneal and conjunctival cells, a growing number of clinical studies suggest that the ocular surface adverse effects caused by PGAs may be minimal. A study compared dry eyes between patients with glaucoma receiving PGAs monotherapy and subjects without glaucoma and showed no significant difference between the two groups [51]. Damage to the ocular surface also varies among different types of PGAs. In a cross-sectional study, Rolle et al. noted that tafluprost did not affect tear stability compared to PF timolol [17]. PGAs showed better tolerability than other antiglaucoma drugs in all of these studies. However, long-term topical application of PGAs can lead to obstructive meibomian gland dysfunction [52]. Agnifili et al. observed PGA-induced morphological changes of the meibomian gland by laser confocal scanning microscopy, which are associated with the development of dry eyes [53].

Effects of Cholinergic Agonists on Ocular Surface

Cholinergic agonists were the earliest used anti-glaucomatous drugs, mainly pilocarpine, reducing the aqueous humor outflow resistance by constricting the pupil and ciliary muscle. The major adverse effect of pilocarpine is miosis, and sometimes with constriction of the visual field, conjunctival irritation, eyelid twitching, blurred vision, and superficial punctate keratitis. Ocular irritation and blurred vision are more pronounced in patients using pilocarpine gel preparations, with incidences of 50% and 70%, respectively. Approximately 20% of patients discontinue pilocarpine therapy because of unacceptable topical adverse effects [54].

Effects of Cholinergic Agonists on Tear Film

A clinical study revealed that 13% of patients treated with pilocarpine for 1 year showed

Schirmer's test value of less than 10 mm, and TBUT of less than 10 s in 27% of patients [55]. Investigators also discovered that pilocarpine significantly suppressed proliferation of meibomian gland epithelial cells in vitro [56].

Effects of Cholinergic Agonists on Cornea

An increased incidence of superficial punctate keratitis and dry eye symptoms due to pilocarpine has been widely reported. Twenty percent of patients using pilocarpine gel suffer from superficial corneal haze, which persists after discontinuation of the drug [54]. Topical application of pilocarpine has also been associated with corneal limbal infiltrates and limbal ulcers, causing the classic allergic limbal keratitis [57]. Animal studies have shown that pilocarpine causes corneal endothelial dysfunction. In a study analyzing the effects of pilocarpine on healthy rabbit corneal endothelial cells, pilocarpine stimulation led to ultrastructural changes in cell contraction, nuclear heterochromatin margination, and cytoplasmic vacuolization [58].

Effects of Cholinergic Agonists on Conjunctiva

Pilocarpine causes changes in the conjunctiva. Cholinergic agonists can induce follicular conjunctivitis and cicatricial pemphigoid. Increased numbers of desmosomes, basal layer changes, and ablation of the intrastromal vascular lumen are visible on microscopic histological sections. In a clinical study, conjunctival impression smears suggested that moderate loss of goblet cell occurred in 32% of patients after 1-year pilocarpine treatment, with squamous metaplasia and inflammatory infiltration in 41% of patients [55]. This may be related to increased expression of matrix metalloproteinases and ECM remodeling imbalance induced by topical application of pilocarpine [59]. Cholinergic agonists also cause significant shortening of the inferior conjunctival vault. However, oral pilocarpine treatment seems to benefit goblet cells and conjunctival epithelium [60].

Effects of α -Adrenergic Agonists on Ocular Surface

α -Adrenergic agonists mainly include drugs such as apraclonidine and brimonidine. The most common reasons for discontinuing α -adrenergic agonist treatment are ocular discomfort, congestion, foreign body sensation, photophobia, and eyelid retraction. Tachyphylaxis and high allergy rate of apraclonidine limit its effectiveness as a long-term treatment. Brimonidine reduces aqueous humor production and increases aqueous humor outflow via the uveoscleral pathway to lower IOP. The most common adverse effects associated with brimonidine are conjunctival reactive hyperemia, allergic blepharo-conjunctivitis, and ocular pruritus [61]. Compared with apraclonidine, brimonidine exhibits a lower incidence (25%) of allergic reactions and no tachyphylaxis. However, brimonidine may increase the potential for allergy to subsequently administered agents, particularly timolol, brinzolamide, and latanoprost [62]. In a large prospective study, approximately 7–14% of patients quit treatment with brimonidine because of ocular allergic reactions [63].

Effects of α -Adrenergic Agonists on Tear Film

A clinical study investigated the short-term effect of topical antiglaucoma medication on tear film within 90 min. Brimonidine showed the most significant reduction of tear basal secretion, and latanoprost caused the most significant reduction in TBUT [64]. After 1-year treatment with brimonidine, 9% and 18% of patients exhibited poor Schirmer's test score and reduced TBUT, respectively [55]. This may be related to allergic reactions to brimonidine. A retrospective study found that tear film production was significantly decreased in the brimonidine-allergic group when compared with the non-allergic one [65].

Effects of α -Adrenergic Agonists on Conjunctiva

α -Adrenergic agonists have clear conjunctival effects, which are more obvious than those of PGAs, but less harmful to goblet cells than β -

adrenergic blockers are. Conjunctival congestion and conjunctivitis occur in approximately 11.0–13.9% of patients using brimonidine, and these are the most common adverse effects of the drug and the most common reason for patients to discontinue the drug [66]. A retrospective medical record review study found 15 suspected cases and four confirmed cases with conjunctival lymphoproliferative disease among 208 patients after topical brimonidine use [67]. After 1-year treatment with brimonidine, 23% and 36% of patients exhibited loss of goblet cell and squamous metaplasia, respectively [55]. Clinical cytological analysis suggested that brimonidine induced more inflammatory responses (in approximately 55% of patients) among four kinds of anti-glaucomatous medications. An animal study suggested that the increase of inflammatory cytokines in the aqueous humor after long-term brimonidine treatment may contribute to the pathogenesis of brimonidine-induced conjunctivitis and uveitis [68].

Effects of Carbonic Anhydrase Inhibitors on Ocular Surface

Currently, the two main anti-glaucomatous CAIs in common use are dorzolamide and brinzolamide, which reduce IOP by inhibiting carbonic anhydrase in the ciliary epithelium to reduce aqueous humor outflow. The most common ocular surface damage caused by the treatment with CAIs includes temporary blurred vision (3–8%) and discomfort (1.8–5.9%), followed by hyperemia, blepharitis, dry eye, and tearing with less than 3% incidence rate [61]. Patients appear to tolerate brinzolamide better than dorzolamide. Switching from dorzolamide to brinzolamide decreased the incidence rate of ocular irritation by 43% [69]. It has been proposed that the physiological pH of brinzolamide compared to lower pH of dorzolamide may improve tolerability and adherence [70].

Effects of CAIs on Tear Film

The topical application of CAIs can also lead to decreased tear film stability. Using a tear film stability analysis system and functional visual

acuity measurements, Noguchi et al. found that topical application of brinzolamide can cause tear film instability, leading to blurred vision [71]. A prospective study found that basal secretion (Jones test) was reduced by 17.3% at 90 min after application of dorzolamide [64].

Effects of CAIs on Cornea

Corneal decompensation caused by CAIs has been reported in several cases [72–74]. Topical dorzolamide and brinzolamide cause damage to the corneal endothelium and a significant increase of CCT, possibly due to the inhibition of corneal transparency maintained by carbonic anhydrase isoenzymes [75]. Dorzolamide can slightly reduce corneal sensitivity and may be associated with its corneal epithelial cell toxicity, with up to 15% of patients progressing to superficial punctate keratitis [76]. However, a clinical study reported that 18 months of brinzolamide treatment did not affect corneal thickness or corneal endothelium cell density [77].

Effects of CAIs on Conjunctiva

Conjunctival congestion is the most common side effect associated with the use of CAIs. Conjunctival congestion has been reported in up to 20.7% of patients after dorzolamide application [78]. Dorzolamide also causes conjunctivitis after approximately 3–12 months of treatment, leading to discontinuation of the drug in 4% of patients [79]. Conjunctival follicles at the corneal limbus have also been reported after topical dorzolamide application [80].

Effects of Rho Kinase Inhibitors on Ocular Surface

Rho kinase inhibitors are another novel medication to lower IOP; they show remarkable therapeutic efficacy in glaucoma but also have common topical adverse effects. A systematic review of 10 studies showed that the most common ocular surface damage caused by Rho kinase inhibitors was conjunctival congestion (19–65%), followed by conjunctival hemorrhage (6–20%) and corneal rotavirus (13–26%)

[81]. Bhargava et al. also found that netarsudil and ripasudil may result in reticular epithelial corneal edema [82]. However, only 12 eyes were included in this study. More clinical and basic research needs to be conducted to figure out the specific effects of Rho kinase inhibitors on the ocular surface.

EFFECTS OF THE PRESERVATIVE BAK IN ANTI-GLAUCOMATOUS MEDICATIONS ON OCULAR SURFACE

Preservatives play an important role in the formulation of topical ophthalmic medications, with their primary role being to provide antimicrobial activity to maintain sterility. However, many preservatives can also cause damage to ocular tissues, especially in the case of long-term use. In general, the antimicrobial activity of a preservative is inversely proportional to its compatibility with the ocular surface. BAK is a quaternary ammonium compound with bacteriostatic, bactericidal, and surfactant properties and is the most commonly used preservative in ophthalmic preparations, including anti-glaucomatous medications. BAK interacts with bacterial cell membranes, resulting in membrane instability and cell lysis. However, BAK is not selective in its action on cell membranes. It can also damage epithelial cells of the ocular surface by the same mechanism. BAK also acts as a corneal permeation enhancer, enhancing the ocular permeability of the active ingredient in BAK-preserved formulations. The threshold concentration of action of BAK is approximately 0.005%. As a preservative in topical ophthalmic preparations, its concentration is approximately 0.004–0.02%. The cytotoxic effects of BAK on ocular tissue cells have been extensively studied, and the total “dose” of BAK (number of drugs, number of drops per day, duration of treatment, etc.) correlates with the prevalence and severity of OSD in patients with glaucoma [83]. Toxic effects of BAK include reduced tear film stability, corneal and conjunctival epithelium toxicity, and immune sensitivity reactions. BAK has

been proved to reduce the survival of corneal, conjunctival, trabecular meshwork, and ciliary epithelial cells. In patients with glaucoma using BAK-preserved drugs, clinical manifestations of BAK-induced ocular surface toxicity include tingling, burning, foreign body sensation, pruritus, and ocular dryness, tearing, increased surface staining of the conjunctival and corneal epithelium, shortened TBUT, reduced Schirmer test, increased prevalence of punctate keratitis, and poor score of ocular surface disease index (OSDI) [84]. OSDI is a questionnaire asking patients the frequency of specific symptoms, such as dryness, photophobia, redness, and foreign body sensation, and their impact on vision-related functions. In numerous in vitro experiments, BAK can induce cytotoxicity or death in a dose-dependent manner.

Mechanism of BAK-Induced Damage to Ocular Surface

BAK is a quaternary ammonium compound with a positive charge, and mitochondria are the only negatively charged compartment in the cell. So BAK may interact with mitochondria. BAK stimulates conjunctival epithelial cells to produce hydrogen peroxide, leading to partial mitochondrial dysfunction. BAK has also been shown to trigger oxidative stress and mitochondrial fragmentation and to inhibit mitochondrial function [85]. Meanwhile, mitochondrial oxidative stress plays an important role in the development of ocular surface diseases as well as age-related corneal diseases and normal corneal aging.

BAK Damage to Tear Film

BAKs destroy the lipid layer of the tear film, shorten TBUT, and decrease tear film stability. Multivariate analysis showed that each additional use of BAK-containing eye drops trebled the odds of abnormal corneal staining tests and the symptoms improved when BAK was removed. A large cross-sectional study of 9658 patients with glaucoma showed that PF anti-glaucomatous medications had relieved pain or discomfort, foreign body sensation, stinging or

burning sensation, and dry eyes compared to patients using preservative-containing drops [86]. These symptoms were also relieved if patients switched from a preservative-containing formulation to a PF formulation. An Australian study of 375 patients with glaucoma and OSD further confirmed the benefits of switching from BAK-preserved to BAK-free anti-glaucomatous medications [87]. Patients who switch to BAK-free anti-glaucomatous drops experienced less use of tear lubricants, improved ocular symptoms, and TBUT with no change in IOP. A number of studies have examined the clinical differences in OSD between patients taking BAK-containing and BAK-free or PF formulations of the same drug. In a prospective epidemiologic study of more than 4000 patients, the prevalence of OSD was approximately two times higher in patients using BAK-containing formulations than PF formulations, with symptoms including discomfort during drops (43% vs. 17%), burning pain (40% vs. 22%), foreign body sensation (31% vs. 14%), dry eye (23% vs. 14%), tearing (21% vs. 14%), and eyelid pruritus (18% vs. 10%) [58].

Although there is strong evidence that BAK is associated with the development of OSD in patients with glaucoma, conflicting evidence exists. A group of prospective studies that included 85 eyes showed no significant differences in tear function (Schirmer and TBUT) and impression cytology between anti-glaucomatous drops monotherapy with and without BAK [14]. Another prospective trial comparing BAK-containing tafluprost with travoprost containing SofZia had similar rates of punctate keratitis and TBUT; however, this study cannot exclude the toxic effects of SofZia and different PGAs [88].

BAK Damage to Cornea

BAK has a significant toxic effect on the corneal epithelium. Ammar and Kahook compared various preservative formulations in ophthalmic drugs and found that BAK was the most toxic to corneal epithelial cells [89]. BAK can induce corneal epithelial cell apoptosis. Immunohistochemistry showed that exposure

to higher concentrations of BAK resulted in decreased corneal epithelial cell viability, increased apoptosis, enhanced inflammatory response, and impaired cell proliferation [90]. This cytotoxicity of BAK may be related to DNA damage [91]. It has been suggested that low concentrations (0.001–0.005%) of BAK cause cessation of normal cell mitotic activity and oxidative mitochondrial damage leading to apoptosis, while high concentrations (0.01%) cause cells to undergo rapid and violent necrosis in response [92]. Clinical studies suggest that these effects may be partially reversible after cessation of BAK exposure [93]. Lower incidence of punctate corneal epithelial erosions and self-reported adverse events (stinging, burning, and redness) was reported in the BAK-free group when comparing dorzolamide/timolol with and without BAK [94].

In animal models, BAK has been proved to reduce cellular tight junction stability [95]. Ultrastructural analysis reveals disruption of epithelial barrier function due to misalignment of tight junctions and disruption of the actin cytoskeleton [96]. During topical administration of anti-glaucomatous drugs, superficial epithelial cells exposed to BAK undergo swelling and detachment, followed by corneal stromal edema, neuronal loss, and damage to endothelial structures [97]. Ayaki et al. also found that corneal endothelial cell damage resulting from anti-glaucomatous eye drops appeared to depend on the presence of BAK [98]. Meanwhile inflammatory cell infiltration can also be seen in the cornea. And its toxic effects are dependent on both dose and exposure time. In animal experiments, mice treated with BAK (0.2 mg/ml) four times daily for 1 week showed a significant increase in corneal staining and an enhanced inflammatory response [99].

In addition, in a clinical study that included 38 patients, after 78–108 months of IOP-lowering treatment, patients treated with topical anti-glaucomatous drugs presented reduced subbasal nerve numbers and lower density compared to controls. However, corneal cell density was similar in both groups [100]. Another study by Martone et al. included 84 patients with bilateral POAG or high IOP and 20 age-matched healthy patients as controls. Using

confocal microscopy, the authors found that, except patients receiving pure anti-glaucomatous drops, patients receiving long-term topical IOP-lowering therapy exhibited ocular surface changes: significant reduction in epithelial cell density in the superficial corneal layer, activation of stromal keratocytes, enhanced inflammatory response, and reduction of subbasal nerves [101]. A clinical study by Saini et al. also revealed a correlation between reduced nerve number and increased curvature, decreased corneal sensation, and tear production [102]. Also, a clinical study showed that when using commercially available anti-glaucomatous drugs containing different concentrations of BAK, the lowest BAK concentration caused the least epithelial damage [103]. These results suggest that BAK-induced dry eye may be associated with subbasal nerve injury.

Substantial experimental evidence confirms the toxicity of BAK to the corneal surface. However, *in vitro* studies may not accurately mimic real clinical situations. The duration of epithelial cell exposure to BAK in a laboratory setting may not adequately mimic the pharmacokinetic conditions in clinical patients. Although the duration of exposure in experimental models ranged from minutes to days, clinical observations revealed that *in vivo* topical application of BAK resulted in an eightfold dilution of BAK concentration in the tear fluid within only 30 s and a 36-fold decrease after 3 min [104]. The usual concentration of 0.02% BAK will be diluted to 0.00056% or barely detectable within 3 min [105]. Furthermore, it is still unclear whether periocular structures (conjunctival vault, eyelids, and lacrimal structures) in patients with OSD have an effect on BAK clearance.

BAK Damage to Conjunctiva

The conjunctiva plays an important role in the maintenance of ocular surface health. The conjunctival epithelium contains goblet cells that produce mucin to reduce evaporation from the aqueous layer of the tear film, the dysfunction of which may cause or exacerbate dry eyes. The conjunctiva is the major target for the toxic

effects of topical ophthalmic agents. Essentially all types of preservatives cause inflammatory responses in the conjunctiva. Epstein et al. studied the effects of various preservatives on corneal and conjunctival epithelial cells and confirmed that all preservatives cause significant goblet cell toxicity to varying degrees [106]. Among these preservatives, BAK is considered to be the most important cause of conjunctival tissue damage, characterized by increased conjunctival epithelium karyoplasmic ratio, reduced goblet cell density, subconjunctival fibrosis, squamous metaplasia, inflammatory infiltration, and conjunctival epithelial toxicity. Albiets and Bruce found that in patients with OSD, preservatives exacerbated conjunctival inflammation in dry eye, resulting in reduced cup cell density [107]. BAK also leads to impaired mucin production by goblet cells and exacerbates cellular damage. Several studies have reported a decrease in the number of conjunctival goblet cells and an increase in the number of mast cells, fibroblasts, macrophages, and lymphocytes induced by BAK [30]. Huang et al. measured the expression levels of ECM, COX-2, and TGF- β 1/Smad3-related molecules. They demonstrated that BAK-induced subconjunctival fibrosis is the result of COX-2-regulated activation of TGF- β 1/Smad3 signaling [108]. Labbé et al.'s study also demonstrated that the promotion of subconjunctival fibrosis by BAK in anti-glaucomatous medications was associated with increased expression of ECM metalloproteinase inducers and modification of conjunctival ECM remodeling [109].

NEW PRESERVATIVE FORMULATIONS WITH LESS TOXICITY

Many alternative preservatives to BAK have been developed for topical ophthalmic treatment and are generally better tolerated than BAK. The main disadvantage of these preservatives is that they are limited to use in fixed formulations.

SofZia

SofZia is an ionic buffer solution containing borates, sorbitol, propylene glycol, and zinc to create an oxidative antibacterial environment [110]. These components are rapidly degraded upon contact with cations on the ocular surface. SofZia is therefore less cytotoxic to ocular tissue than BAK is [111]. In clinical studies, travoprost with SofZia scored higher on ocular symptoms and quality of life surveys compared to travoprost with BAK [112]. In addition, significant improvements in ocular signs and symptoms of OSD were observed in patients when switching from BAK-containing travoprost to SofZia-containing travoprost. More importantly, given the potential role of BAK in enhancing active ingredient penetration, the IOP control performance remained excellent when BAK was replaced by SofZia [113].

Polyquad

Polyquad is a hydrophilic cationic quaternary ammonium polymer with a similar mechanism of action to BAK, which can disrupt bacterial cytoplasmic membranes. As a result of its large size and lack of a hydrophobic region may prevent it from entering eukaryotic cells, thus reducing its adverse effects on human cells [114]. Polyquad has been used in contact lens solutions and dry eye preparations since the 1980s and is now included in anti-glaucomatous medication formulations [115]. Polyquad exhibits significantly lower cytotoxicity to ocular surface compared to BAK, which is equal to PF preparations [116]. In clinical studies, eyes treated with polyquad-containing travoprost had lower OSDI scores than treated with BAK-containing travoprost. And switching from the BAK-containing formulation to polyquad showed improvements in both OSD signs and symptoms [117]. As with SofZia, replacing BAK with polyquad does not affect the IOP-lowering effect of anti-glaucomatous drug formulations [118].

Purite

Purite contains 99.5% chlorite, 0.5% chlorate, and trace amounts of chlorine dioxide, which are converted to sodium ions, chloride ions, oxygen, and water upon contact with the tear film. The chlorine dioxide radicals in the solution confer antimicrobial activity, effectively against both bacteria and viruses. Purite is less cytotoxic to the ocular surface than BAK is [119]. Clinical studies suggest that in patients with glaucoma and signs or symptoms of OSD, brimonidine preserved with purite was better tolerated than brimonidine preserved with BAK and afforded comparable IOP reduction [120]. In another 12-month randomized, multicenter, double-blind, parallel-group study, patients with glaucoma treated with brimonidine-purite (Alphagan; Allergan, Irvine, CA) 0.15% had a 41% lower incidence of allergic conjunctivitis, a significantly lower incidence of conjunctival congestion, ocular discharge, higher comfort and satisfaction scores than brimonidine-BAK (Alphagan) 0.2% group [121]. Brimonidine-purite causes less corneal injury and conjunctiva inflammatory infiltration than BAK-containing medications [122]. In a study with rabbits, the levels of the drug in aqueous humor were similar after the use of 0.2% brimonidine-BAK and 0.15% brimonidine-purite formulations [123]. In addition, there was no statistical difference in pain, tingling, and blurred vision between the PF and purite formulations of brimonidine used [124]. These results suggest that the brimonidine-purite formulation may exhibit better systemic safety and efficacy than the BAK-preserved formulation, but comparative clinical studies are needed to further confirm its effects.

PRESERVATIVE-FREE FORMULATIONS

Topical ophthalmic treatments for glaucoma and OSD are available in PF formulations such as Timoptic in Ocudose, Cosopt PF, Zioptan, etc. Currently, PF tafluprost is mainly used in China. As expected, these formulations have lower cytotoxicity than their corresponding BAK-preserved formulations. In clinical studies,

the PF formulations showed less severe signs and symptoms of OSD and performed well in terms of IOP control compared to the preservative-containing formulations [84, 86, 125–127]. Several studies have evaluated the clinical efficacy and safety of PF tafluprost [128–132]. And results showed significant reductions of IOP in patients treated with PF tafluprost either initially or by conversion from other PGAs. PF tafluprost is well tolerated and safe, with 97.9% of patients continuing treatment [130]. A meta-analysis showed that PF tafluprost significantly increased TBUT and tear production and significantly improved ocular symptoms compared to latanoprost [125]. A prospective, observer-blind study enrolled 30 patients (60 eyes) with open-angle glaucoma, and revealed that switching from latanoprost to the PF tafluprost significantly increased TBUT and reduced the proportion of abnormal corneal fluorescein staining [133]. Furthermore, after switching from other PGA monotherapy to PF tafluprost, patients had a lower proportion of conjunctival congestion and significantly improved tolerability [128, 129].

However, PF formulations also have limitations. For example, many topical therapies are not available in PF formulations. Single-dose packages are more expensive and carry a greater financial burden for patients. In addition, for many patients, especially the aged with the highest risk of age-related diseases such as glaucoma and OSD, single-dose packages are inconvenient to use, resulting in poorer medication compliance. Multidose packaging can overcome these problems, but there is still a risk of microbial contamination. Multidose PF formulations systems have been developed to prevent microbial influx, such as the ABAK and COMOD systems. PF liposomal ophthalmic sprays have also been developed for the treatment of OSD.

SUSTAINED RELEASE SYSTEM

Drug sustained release (SR) refers to the continuous administration of drugs to target tissues at the expected therapeutic concentration to avoid the peak and trough of pulsed local

administration. A drug delivery system can reduce patients' need for self-administration and improve compliance, so it may improve clinical results and quality of life. At present, a variety of anti-glaucomatous medication delivery systems have entered clinical research, but not to be implemented clinically, including intraocular implants, punctal plugs, contact lenses, nanospheres, etc.

Intraocular Implants

The intraocular implants are mainly placed in the iridocorneal angle. Bimatoprost SR for glaucoma treatment is 10 mg bimatoprost embedded in the poly-D,L-sustained lactide-co-glycolide polymer matrix, which is slowly degraded into water and carbon dioxide, leaving no residue in the eyes. A phase I/II, prospective controlled clinical trial suggested that Bimatoprost SR exhibited favorable efficacy and safety comparable to bimatoprost eye drops within 24 months [134]. The most common adverse events include conjunctival congestion, foreign body sensation, and eye pain, which may result from active pharmaceutical ingredients and implantation procedure. The high loss rate of corneal endothelium is the main problem of this system [135]. iDOSE can constantly release travoprost for 6–12 months. The phase II trial found that iDOSE exhibited an equal IOP reduction effect to timolol [136]. This system showed no adverse effects on conjunctiva and cornea.

Punctal Plugs

Punctal plugs allowing elution of drugs into the tear film are easy to load and unload and well tolerated by patients. OTX-TP is an intracanalicular punctal plug produced by Ocular Therapeutix, consisting of polyethylene glycol hydrogel and brimonidine polylactic acid. OTX-TP showed a 15.6% reduction of IOP in an Asian population [137]. Another punctal plug Evolute loaded with latanoprost showed retention rate of 96% and 5 mmHg reduction in IOP after 12 weeks [138]. These systems help to maintain

tear volume, thus protecting the ocular surface from drug damage.

In addition, other sustained release systems have incorporated many natural polymers into drug delivery vehicles. Drugs can be loaded onto the hydrogel contact lenses, placed on the cornea, and eluted by tear film, so as to improve the bioavailability of the drug increase and increase retention time on the ocular surface. Polymeric hydrogels are also used as biocompatible nanospheres for drug delivery to penetrate the corneal barrier. Currently, this research is still at the stage of animal experiments.

OSD MANAGEMENT FOR PATIENTS WITH GLAUCOMA

During the treatment of glaucoma, it is important to consider not only the effect of medications on IOP but also the incidence and severity of drug-induced OSD. Thirty-eight percent of patients receiving topical monotherapy, 54% of patients receiving two topical treatments, and 71% of patients receiving three or more topical treatments resulted in moderate or severe OSD. The inherent decline in ocular surface condition of the aged makes it important for populations treated with multiple eye drops and the elderly population, in particular, to carry on OSD management [139]. However, it should be emphasized that in daily practice this situation may be more severe than in clinical trial data. The proportion of patients with glaucoma and signs and symptoms of OSD in clinical practice is significantly higher than in prospective clinical trials or the general population [140]. The typical duration of a clinical trial is 6–12 months. During this period, the long-term effects of treatment may go undetected and be underestimated. Thus, the background of drug-induced OSD is usually more severe than demonstrated in clinical trials, and management of OSD in patients with glaucoma is more difficult to improve in clinical practice.

Efficacy and tolerability should always be a prominent consideration in the treatment of glaucoma. Clinical routine evaluation of glaucoma should include assessment of OSD signs and symptoms. A thorough ocular surface

examination should be performed on every patient with glaucoma before starting topical treatment and during follow-up. A number of routine examinations can readily identify OSD, such as dryness or burning sensation, foreign body sensation, eyelid congestion, meibomian gland dysfunction, shortened TBUT, corneal or conjunctival fluorescein staining, and the need for artificial tears.

In addition, given the frequency and severity of ocular toxicity associated with the topical use of anti-glaucomatous medications, particularly BAK, the European Medicines Agency recommends that preservatives be avoided for patients who are intolerant of preservative-containing eye drops and in patients with long-term therapy. It is recommended to use the lowest concentration consistent with antimicrobial function in a stand-alone formulation. For patients using multiple BAK-containing formulations, there is an option to switch to a fixed combination formulation to reduce BAK exposure through lessening the total number of drops administered per day [141].

Use of Less Frequent Dosing Agent

It is important to note that not all patients are sensitive to preservatives and not all topical adverse effects of IOP-lowering medications are caused by preservatives. Given that both increased frequency of dosing and co-administration are risk factors for the development of OSD in patients with glaucoma, the use of less frequent dosing agents (e.g., PGAs, once daily) is recommended. PGAs have been increasingly used as first-line or preferred anti-glaucomatous medications because of their high efficiency in lowering IOP, lack of significant systemic adverse effects, once-daily dosing, and excellent overall tolerability. Special attention should be paid to patients with glaucoma who have existing OSD or who develop dry eyes or ocular irritation over time. Once OSD has developed, the option of changing to another more tolerable medication, using a PF formulation, or opting for surgery or laser treatment may be available on an individual basis.

Fixed Combination Formulation

Compared to generic formulations, fixed combination formulations offer higher efficacy in lowering IOP, reduce preservative exposure and risk of preservative-related OSD symptoms, eliminate washout associated with inadequate interval between drops, and decrease the total number of drops. In addition, the fixed combination formulation improves treatment compliance and persistence owing to the simplification of the eye drop strategy, resulting in improved stability of IOP control [142]. A meta-analysis of randomized clinical trials comparing three fixed combination formulations of PGAs and timolol showed that the combination therapy displayed a more pronounced IOP-lowering effect than the respective PGAs or timolol components [143]. Several randomized, double-blind, controlled, prospective clinical studies have shown that the IOP-lowering effect of fixed combination formulations is comparable to that of the corresponding non-combination agent therapy [144–146]. Two 6-month randomized double-blind prospective phase III clinical trials investigated the IOP-lowering efficacy, ocular tolerability, and safety of the fixed combination formulation of tafluprost and timolol. The formulation showed good IOP-lowering effects and fewer adverse events, with conjunctival congestion being the most common adverse event during treatment at 4.8–9.5% [147, 148]. In another study, the PF tafluprost/timolol fixed combination had a lower incidence of ocular congestion (6.4–8%) and ocular irritation (7–12.4%). So, the short-term tolerability of the combination may depend on the action of the IOP-lowering active ingredient itself [149].

Ocular Surface Protective Medication

Artificial Tears

Artificial tears are the main treatment for dry eyes. Artificial tears improve tear film stability, protect the cornea, and reduce pressure of the ocular surface, thereby improving quality of life. There are currently various preparations based on polyvinyl alcohol, povidone, hydroxypropyl

guar gum, cellulose derivatives, and hyaluronic acid. These preparations have a branching structure similar to that of mucin and can maintain and replenish the tear film, thereby improving dry eyes symptoms. In principle, PF medications are recommended for OSD. The results of a systematic review showed that these drugs significantly improved dry eye signs, but there were no clear statistical differences among different product types. Generally, less viscous artificial tears, such as 0.1% sodium hyaluronate and 0.5% carboxymethyl cellulose, are indicated for mild dry eyes. Patients with moderate to the severe dry eyes should use artificial tears with higher viscosity such as 0.3% sodium hyaluronate and 1% carboxymethyl cellulose [150]. Clinical studies have shown that artificial tears containing lipid components are superior in improving signs of patients with moderate to severe dry eyes compared to formulations containing hyaluronic acid. Especially in patients with meibomian gland dysfunction, these artificial tears have also shown better improvement in TBUT [151]. Carbomer in situ gel systems undergo a solution-gel shift when in contact with the ocular surface, which helps increase the residence time of artificial tears and are mainly used for severe dry eye. However, they are often used at bedtime because they can cause blurred vision and eye discomfort. Therefore, the choice of artificial tears is based on the type and degree of dry eye, patient compliance, and comfort.

Promoting Tear Production

Diquafosol sodium promotes the repair of ocular surface damage by promoting aqueous tear secretion, mucin secretion from conjunctival goblet cells, and increasing the thickness of the lipid layer by protecting the function of the meibomian gland [152]. A study enrolled 138 patients with glaucoma with dry eye disease who received topical anti-glaucomatous drops for more than 6 months. Treatment with 3% diquafosol sodium resulted in stable IOP, improved subjective ocular surface symptoms OSDI, prolonged TBUT, increased tear production, and improved goblet cell counts [153]. Another study including 46 patients with 84 eyes with primary normal IOP glaucoma also

showed that 3% diquafosol sodium drops protected the meibomian gland morphology in patients with long-term use of PGA-containing preservative [154].

Facilitating Ocular Surface Repair

The active ingredients of pro-ocular surface repair eye drops are mainly epidermal growth factors and fibroblast growth factors, which can promote epithelial cell proliferation and improve the microenvironment of the ocular surface. In addition, studies have shown that dry eye is associated with oxidative stress. So, antioxidants or free radical scavengers such as vitamins A, E, and B₆ have been used to treat dry eye. A clinical study showed that the addition of vitamin A to tear substitutes improved dry eye symptoms [155]. However, in animal models, vitamin A has also been shown to cause meibomian gland dysfunction [156]. And vitamin A is very unstable in liquid formulations and poorly tolerated by patients. In addition, the lipoic acid may improve tear film stability [157].

Ophthalmic Serum Preparations

Ophthalmic serum preparations, mainly consisting of autologous serum and calf serum deproteinized extract, are rich in growth factors that promote ocular surface epithelial repair and nerve regeneration, and maintain the ocular surface microenvironment. They are applicable to moderate to severe dry eye with ocular surface damage and corneal pain. In a clinical study, calf serum deproteinized extract was shown to be more effective than 0.3% sodium hyaluronate drops in relieving eye pain and photosensitivity in patients with dry eye [158].

Surgical Treatment

Drug therapy is the first-line method for glaucoma treatment. When a drug therapy performs poorly in IOP control or can not stabilize disease progression, surgical treatment can be taken into account. Although OSD caused by glaucoma filtration surgery is common, given that the long-term use of anti-glaucomatous medications and topical steroid infusion after

surgery may have a positive impact on the ocular surface status, surgical treatment is still beneficial to reduce OSD [159, 160]. A 1-year follow-up study showed the improved conjunctival state, the decreased level of pro-inflammatory protein, and the enhanced function related to lipid transport in patients after trabeculectomy [161]. In addition, selective laser trabeculoplasty or minimally invasive glaucoma surgery may be a more appropriate choice for patients with glaucoma and OSD. This kind of surgery avoids or reduces conjunctival injury, thus alleviating postoperative inflammatory response and ocular surface irritation [162].

CONCLUSION

Anti-glaucomatous medications remain the preferred treatment option for many types of glaucoma. The ensuing OSD needs to be considered by physicians, especially in patients using multiple anti-glaucomatous medications and geriatrics. Evaluation of the ocular surface should be included as a routine part of the follow-up of patients with glaucoma. Ocular surface disease resulting from glaucoma medications mainly occurs in the cornea, conjunctiva, and meibomian glands. And changes of the ocular surface microenvironment are associated with patient compliance with treatment as well as treatment outcomes and quality of life. Comprehensive management of the ocular surface is needed for patients with glaucoma. And medications with good IOP-lowering effects and requiring less frequent use (such as PGAs and fixed combination formulations) should be selected as much as possible to improve the quality of patients' ocular surface environment. The ideal anti-glaucomatous drug is one that is only mildly damaging to the ocular surface tissue and maintains drug activity, containing a new preservative with less toxicity or PF preparations, even with a sustained release system. For patients who have developed OSD, additional treatment with ocular surface protective medication may be considered to improve the overall ocular surface structure by stabilizing the three layers of the

tear film. Laser and surgical treatments are also options if necessary.

ACKNOWLEDGEMENTS

Funding. This work was supported by the National Natural Science Foundation of China [Grant Numbers 81970801 to XD]; the Hunan Province research and development plan funding projects in key areas [Grant Numbers 2020SK2133 to XD]; the Science and Technology Foundation of Changsha, Hunan, China [Grant Numbers kh1801229 to XD]; the Natural Science Foundation of Hunan Province, China [Grant Numbers 2019JJ40001 to XD]; and the Science and Technology Foundation of Aier Eye Hospital Group, China [Grant Numbers AR1906D1, AM1906D2 to XD]. The National Natural Science Foundation of China is funding the journal's Rapid Service Fees.

Editorial, Medical Writing, and Other Assistance. The authors wish to thank China Santen Medical Affairs [China Santen Medical Affairs, Santen Pharmaceutical (China) Co., Ltd.] for providing assistance.

Author Contributions. Xuanchu Duan proposed and designed the study. Xinyue Zhang searched the literature. Xiaoyu Zhou drafted the manuscript. Dengming Zhou and Yang Zhao revised the manuscript. All authors read and approved the final manuscript.

Disclosures. Xiaoyu Zhou, Xinyue Zhang, Dengming Zhou, Yang Zhao and Xuanchu Duan confirm that they have no conflicts of interest to declare.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this

published article/as supplementary information files.

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