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Ocular Surface Disease and Glaucoma Medications: A Clinical Approach

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Abstract

Objectives—Ocular surface disease frequently co-exists with glaucoma and may be initiated or exacerbated by topical glaucoma medications. We performed a review of current literature to assess the prevalence, causes, and treatment of ocular surface disease in glaucoma patients, specifically those on topical therapy.

Methods—A Pubmed database search was conducted. A total of 720 articles published from 1972 to 2018 were found in relation to ocular surface disease, glaucoma, and glaucoma medications. Of these, 102 articles were included in this analysis. We included primary and empirical studies for patients on topical glaucoma medications. Exclusion criteria included case reports, non-English studies, and articles unrelated to the primary subject of this review.

Results—Ocular surface disease among normal and glaucomatous eyes was evaluated based on diagnostic testing including clinical exam and questionnaires to determine visual function and quality of life. Glaucoma medications can be associated with toxicities to the ocular surface, most often due to the nature of the preservative included in the medication; however, the incidence of toxicity can be mitigated by the use of preservative free medications, decreased preservative medications, or treatment of dry eye disease. Treatment of glaucoma with laser trabeculoplasty or minimally invasive glaucoma surgeries that spare the conjunctiva and the cornea may avoid or decrease reliance on topical glaucoma medications, potentially avoiding the initiation or progression of ocular surface disease.

Conclusions—Recognition and treatment of ocular surface disease in glaucoma patients may improve patient quality of life and medication adherence. This may ultimately improve glaucoma treatment outcomes.

Keywords

ocular surface disease; topical medications; glaucoma

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Introduction

Ocular surface disease is a multifactorial disorder of the conjunctival epithelium, corneal epithelium, lacrimal glands, and meibomian glands that results in either deficient or inappropriate tear production and leads to decreased visual clarity and ocular discomfort through various inflammatory pathways[1,2]. Ocular surface disease can occur in conjunction with many other ocular conditions, and here we aim to focus on the coexistence of ocular surface disease with glaucoma.

Glaucoma is the second leading cause of blindness in the world and is expected to affect 79.6 million people by 2020. At present, 11% of the 5 million Americans over 50 who have dry eye disease also have glaucoma[3–6]. Topical medical therapy is the most common initial treatment for glaucoma, and 49-59% of glaucoma patients on topical anti-glaucomatous medications have ocular surface disease[7–9]. Ocular surface disease in these patients can be a pre-existing condition that is exacerbated by topical therapy or a novel disease that manifests after initiation of topical glaucoma therapy. Topical glaucoma medications can cause burning, irritation, itching, tearing, and decreases in visual acuity within three months of medication initiation[2,11,12] .

Furthermore, untreated primary open angle glaucoma (POAG) patients have a higher risk of ocular surface disease in part due to a 22% lower basal tear turnover rate in comparison to patients without glaucoma[13]. The resulting ocular surface disease in patients with glaucoma can lead to poor medication compliance from the associated symptoms. In addition, ocular surface disease is also linked to a higher rate of failure in subconjunctival glaucoma surgery[14–18]. Thus, management of ocular surface disease in glaucomatous patients is important when trying to reduce further ocular morbidity and to improve the success of glaucoma therapy. We have performed a systemic review of the literature to describe the occurrence of ocular surface disease in conjunction with topical glaucoma medical therapy and the management of glaucoma when ocular surface disease exists.

Methods

A literature review was performed in collaboration with a research librarian using the PubMed Database to gather a complete list of studies in relation to ocular surface disease and glaucoma therapy. The PubMed database was searched using the following terminology: prevalence and epidemiology of ocular surface disease in glaucoma, preservative versus preservative-free eye drops, alternative treatments in ocular surface disease, alternative treatments in glaucoma, and glaucoma medication intolerance. In total, 720 articles published between 1972 to 2017 were reviewed and included or excluded from this analysis based on predetermined criteria. The titles and abstracts of the above studies were reviewed, and 95 studies were deemed appropriate to be included in the review. Inclusion criteria included primary and empirical studies of patients with glaucoma who are on topical glaucoma therapy. Exclusion criteria included animal studies that were not directly relevant to the subject matter, case reports, non-English language studies, and papers irrelevant to ocular surface disease and glaucoma.

Results

Current common therapies for the topical management of glaucoma include the use of prostaglandin analogs, beta-adrenergic antagonists, alpha-adrenergic agonists, and topical carbonic anhydrase inhibitors. Due to either the added preservative or the active ingredient of the medication itself, all of the above standard topical treatments for glaucoma can cause or worsen ocular surface disease. As the number of glaucoma medications required increases, both the prevalence and severity of dry eye also increase[14,19–26]. Correspondingly, ocular surface disease appears to increase in severity as the duration of therapy increases[11,25]. A large proportion of glaucoma and ocular hypertensive patients require multiple topical intraocular pressure (IOP) lowering agents, and 49% of ocular hypertensives will require at least two topical medications within five years of diagnosis, thus increasing the risk of ocular surface disease.

Each medication class has specific potential adverse effects on the cornea and ocular surface. Prostaglandin analogs are associated with both a higher prevalence and severity of obstructive meibomian gland dysfunction[27]. Furthermore, prostaglandin analog therapy was shown to cause a higher rate of meibomian gland dysfunction in patients already receiving non-prostaglandin analog ocular hypotensive therapy, possibly worsening ocular surface disease[27,28]. Beta blockers act on beta receptors in the lacrimal gland and reducing basal tear turnover rate[29,30]. Timolol has been found to alter the mucus composition in the tear film and also cause increased staining of the cornea and conjunctiva after one month of therapy[31,32]. The commonly used alpha-adrenergic agonist brimonidine tartrate has a significantly higher incidence of ocular allergy compared to other topical medications and may predispose patients to ocular allergy from additional topical antiglaucoma drops[33]. The carbonic anhydrase inhibitor dorzolamide has been found to increase corneal thickness, but the effect of dorzolamide on the corneal endothelium is still in question[34]. *In vivo* studies of human corneal epithelial cells show that pure glaucoma medications may decrease the viability of the corneal epithelial cells and have the capacity to induce apoptosis through C/EBP homologous protein recruitment[35].

Pathology of Drop Toxicity

The pathology of drop toxicity can be a result of changes in various inflammatory pathways. Patients treated with long term topical antiglaucoma medications prior to glaucoma surgery had conjunctival and Tenon’s capsule biopsies with significantly more macrophages, mast cells, and lymphocytes compared to patients who only had primary glaucoma surgery, suggesting that antiglaucoma medications increase conjunctival inflammation[36]. Conjunctival cells of patients on multi-drug topical treatment for glaucoma showed significantly greater HLA-DR expression as compared to those on monotherapy[37]. Prolonged topical treatment for glaucoma significantly increased ocular surface inflammatory marker expression compared with untreated eyes, specifically IgE and Class II antigen HLA-DR[17,28,37–39]. Thus, both duration and quantity of topical antiglaucoma therapy are correlated with increased histological inflammation. These histological changes may explain clinically significant, toxicity-related symptoms including ocular hyperemia, chemosis, pruritis, periorbital edema, and erythema[40,41].

Preservatives are regularly added to glaucoma medications at the lowest concentration possible to prevent microbial contamination of the drops[42,43]. At present, preservatives used in glaucoma medications include benzalkonium chloride (BAK), the sofZia preservative system [Alcon Laboratories, Fort Worth, TX] used in Travatan Z [Alcon Laboratories, Fort Worth, TX], stabilized oxychloro complex [Purite, Bio-Cide International Inc., OK, USA] used in Alphagan P [Allergan, Irvine, CA], and polyquaternium-1 [Polyquad, Alcon Laboratories, Fort Worth, TX] used in Travatan formulations outside the United States[Alcon Laboratories, Fort Worth, TX][42,43,43]. In general these preservatives target bacterial cell walls and can increase drug penetration in the cornea[42–48].

BAK, the most commonly used of these preservatives, has also been indicated in initiating or worsening ocular surface disease (Table 1). BAK is weakly allergenic with both time and dose-dependent toxicity on the conjunctiva and cornea. It may initiate or worsen ocular surface disease by destabilizing goblet cells and, subsequently, the tear film by inducing squamous metaplasia of the conjunctival epithelium, disrupting the corneal epithelium by reducing epithelial cell density, and increasing stromal keratocyte activation[15, 29,42,49–51]. Animal studies have shown that medications containing higher levels of BAK resulted in greater corneal damage and conjunctival infiltration than those preserved with Purite or lower levels of BAK[52]. Ocular surface effects are dependent on concentration, and low concentrations of BAK have been found to be similar in surface toxicity to newer preservatives in the same medication[53]. In comparison to BAK, one study found that Polyquad, Purite, and the sofZia preservative system have less toxic effects on the ocular surface with sofZia having the least amount of toxic effects[40]. However, while newer preservatives and lower concentration of BAK may result in less ocular surface toxicity, these additives are also less effective in inhibiting microbial growth in medications[54]. Thus, the benefits of ocular surface toxicity must also be carefully measured against drop safety for patients to gain the most benefit from these medications.

Diagnostic Testing to Monitor Ocular Surface Complications

Determination of the effect of glaucoma drops on the ocular surface can be evaluated through clinical exam as well as through functional questionnaires to quantify the effects of ocular surface disease on patient quality of life. Slit lamp exam can reveal ocular surface issues with vital dye staining, determination of tear breakup time, Schirmer’s testing, conjunctival reaction, meibomian gland dysfunction, and evaluation of the corneal epithelium (Figure 1).

Each additional drop of BAK-containing medication can double the likelihood of abnormal lissamine green staining[20]. One study found that patients on antiglaucoma medications with preservatives had significantly decreased Schirmer’s and tear break up time compared to those on preservative free glaucoma drops[29]. As the duration and number of topical glaucoma medications increases, tear break up time, Schirmers I testing, and corneal staining showed worsening signs of ocular surface damage[25].

Quality of life can be determined with the use of the Ocular Surface Disease Index [OSDI questionnaire; Allergan, Irvine, CA], a 12 item questionnaire created to estimate the effect of dry eye symptoms on daily visual function and with the use of the Glaucoma Quality of

Life-15 (GQL-15) form, a 15 item questionnaire created to estimate the impact of glaucoma on daily visual function[14,55,56]. Prior studies have used the OSDI questionnaire as a measure of ocular discomfort, function, and environmental triggers[55,56]. Higher OSDI scores in general are associated with worsening ocular surface symptoms and can be attributed to toxicity at the ocular surface, but higher scores may also be attributed to advancing visual field loss in glaucoma patients[14,55,57,58]. Lower GQL-15 scores are associated with more severe glaucoma and higher OSDI scores[14]. With respect to preservatives, BAK containing drops were more likely to result in abnormal OSDI scores than drops without BAK[59]. A daily dose of more than three BAK-containing drops was an independent risk factor for a higher OSDI score (Odds ratio: 2.61, 95% CI 1.52-4.48)[14]. Ultimately, determination of the specific effect of dry eye on the quality of life of glaucoma patients is difficult as both conditions can adversely affect visual function and quality of life.

Management of Ocular Surface Disease in Conjunction with Glaucoma Medications

Alternatives to conventional topical glaucoma therapy include alternative medications such as preservative free topical medications or surgical/procedural alternatives such as laser trabeculoplasty, minimally invasive glaucoma surgery, or novel forms of drug delivery that may result in improved outcomes for both ocular surface disease and glaucoma. Worsening of the ocular surface in patients with a history of ocular surface disease, conjunctivochalasis, or in elderly patients more susceptible to dry eye disease can lead to increasing patient anxiety and depression[60,61]. This change in mood can result in poor medication adherence and may in turn contribute to advancing glaucomatous disease[14,15,21,49,62]. Approximately 23 to 59% of patients on topical therapy can be non-adherent to prescribed treatment regimens[63]. Alternative options that can improve patient quality of life and medication compliance can include medical management using drops with less toxicity, intensive ocular surface disease treatment, and surgical management with both noninvasive glaucoma procedures and minimally invasive glaucoma surgery.

Medical Management

Prevention of ocular surface disease in patients on topical glaucoma therapy can be achieved by reducing exposure to BAK. This may involve the use of preservative free medications, glaucoma medications with a lower amount of BAK, alternative preservatives, or concurrent treatment of ocular surface disease. Reducing the eye's exposure to surface damaging preservatives is the goal when attempting to prevent worsening of ocular surface disease and improving adherence to topical medications[16,17,18,64].

Currently, most available generic eye drops in the United States contain BAK as a preservative. Recently, preservative-free formulations of glaucoma medications have become more popular to avoid the ocular surface irritation induced by BAK and other preservatives, and studies comparing the effectiveness of these formulations have shown an improvement in ocular surface symptoms when patients switched from BAK-preserved medications to preservative free glaucoma medications[24,25,26,29,59,65–67]. One study found that pain during drop instillation, foreign body sensation, burning, and dry eye sensation were significantly

decreased in patients using topical preservative free beta blocker carteolol in comparison to BAK preserved carteolol[65]. Subjects in the BAK preserved carteolol group also had decreased TBUT from baseline, whereas those on preservative free carteolol had no change in TBUT[65].

Higher BAK concentration in glaucoma medication has been found to be associated with greater ocular surface toxicity, and lower BAK concentration in glaucoma drops can result in a lower rate of ocular surface disease. A study in Japan found that a lower concentration of BAK in tafluprost ophthalmic solution (0.001%-0.003% compared to the normal 0.005%-0.01%) resulted in a level of corneal epithelial cell cytotoxicity comparable to preservative free tafluprost[68]. Similarly switching from latanoprost with 0.02% BAK, bimatoprost with 0.005% BAK, or tafluprost ophthalmic solution with 0.005%-0.01% BAK to tafluprost with 0.001%-0.003% BAK resulted in a significant reduction in superficial punctate keratitis at twelve weeks[68].

BAK free preparations that utilize alternative preservatives have been shown in studies to result in improved ocular surface disease. Patients using polyquaternium-1 preserved travoprost had significantly lower OSDI scores at three months and six months compared to patients using BAK preserved travoprost, indicating a higher level of visual comfort and function with use of the alternative preservative[69]. SofZia reacted with cations on the ocular surface and formed non-toxic byproducts that resulted in less superficial punctate keratitis than BAK preserved travoprost[40,70]. Switching from BAK preserved latanoprost and bimatoprost to sofZia preserved travoprost (Travatan – Z; Alcon Laboratories, Fort Worth, TX) was noted to reduce OSDI scores, decrease conjunctival hyperemia, and improve visual acuity[71]. Of note, studies with BAK preserved and preservative free tafluprost, travoprost, betaxalol, topical 2% carteolol, and 0.1% timolol gel revealed no difference in terms of amount and duration of IOP reduction between preserved and preservative-free versions of the same topical medication [39,72–76].

Glaucoma medications with non-BAK preservatives and preservative free topical medications are not available in generic formulations in the United States, potentially increasing drug costs for patients[40,69]. One study created a questionnaire-based approach on recommending preservative free glaucoma treatments only to patients with a TBUT less than 10 seconds, marked corneal staining, hyperemia, and OSD complaints. This method may improve patient selection if cost is a barrier in patient care[77]. Notably, preservative free drops may have an increased risk of contamination especially in older patients who may have difficulty with appropriate drop instillation[78]. If no alternative is possible other than a BAK containing antiglaucoma medication, prostaglandins may be preferable because some evidence has suggested that these drops may cause less damage to the conjunctiva[79,80].

Finally, maximizing the health of the ocular surface may be another treatment option that is viable for some patients. Utilizing artificial tears with sodium hyaluronate or hydroxypropyl-methycellulose/dextran, both ocular surface lubricants, can provide some relief of ocular surface disease symptoms. In a trial comparing safety and efficacy of hydroxypropyl-methycellulose/dextran with 0.18% sodium hyaluronate, glaucoma patients with ocular surface disease who used 0.18% sodium hyaluronate showed significantly more

improvement in mean OSDI score, lid margin inflammation, and conjunctival injection[81]. For patients who are tolerant to BAK preserved anti-glaucoma medications, adding sodium hyaluronate containing artificial tears as an adjunct appears to decrease OSDI scores, increase goblet cell density, and increase TBUT[82–84]. Furthermore, visual field test parameters were improved in patients using artificial tears, highlighting the impact of a stable tear film and healthy corneal surface[1].

Another preventative and ocular surface modifying measure in mild to moderate dry eye disease is the use of topical cyclosporine 0.05% twice daily in conjunction with glaucoma drops[29]. Topical cyclosporine 0.05% has been found to be beneficial for ocular surface symptoms following a trabeculectomy[16]. In glaucoma patients on chronic topical glaucoma therapy, taking topical cyclosporine for 6 months was found to significantly improve their sub-basal nerve fiber layer density and corneal sensitivity, helping to reverse the adverse surface toxicity from preserved anti-glaucoma medications[29,85].

While studies are preliminary, additional supplements forskolin, vitamin A, and carbomer may benefit glaucoma patients with ocular surface disease. Forskolin is a plant-based product seen to induce conjunctival accessory lacrimal gland secretion and decrease intraocular pressure by reducing aqueous humor production through activation of the ciliary epithelial adenylate cyclase receptor complex[86,87]. Forskolin with rutin, vitamin B1, and vitamin B2 taken for thirty days was found to improve dry eye symptoms in 38 patients with POAG on chronic glaucoma medications by decreasing their OSDI score, increasing Schirmer's test scores, and increasing TBUT[86]. Further studies are required to assess the specific effects of forskolin on both the ocular surface and intraocular pressure. In patients on long-term prostaglandin analogues, preliminary studies show that vitamin A palmitate and carbomer gel appeared to relieve dry eye symptoms by increasing conjunctival goblet cell density[88], though larger studies are required for further assessment of this supplement.

Surgical Management

Practitioners treating glaucoma patients who have concomitant ocular surface disease should consider alternative ways to lower intraocular pressure to minimize potential ocular surface effects from topical medications. Studies have determined that laser trabeculoplasty is an effective first line therapy for glaucoma[89]. Specifically, the Glaucoma Laser Trial determined that argon laser trabeculoplasty was as effective as topical timolol for the first line treatment of glaucoma. Laser trabeculoplasty has the dual benefit of decreasing medication noncompliance as well as decreasing the incidence of ocular surface disease by potentially lowering the medication burden. Newer laser studies using micropulse diode laser trabeculoplasty (MDLT), titanium sapphire laser trabeculoplasty (TLT), pattern scan laser trabeculoplasty (PLT) are currently under investigation, and may broaden the clinical scope of laser trabeculoplasty and further glaucoma treatment[90–92].

Filtration surgery may aid in better controlling glaucoma by decreasing the topical medication burden; however, patients post-glaucoma surgery can also experience conjunctival scarring and chronic ocular irritation[16–18,93] (Figure 2). The Collaborative Initial Glaucoma Treatment study (CIGTS) evaluated the benefits of initial trabeculectomy treatment versus topical medical treatment and found that patients undergoing

trabeculectomy had a higher rate of ocular irritation at five years while other studies have found no difference in dry eye symptoms between patients on chronic anti-glaucoma medications and those who had undergone trabeculectomy[67,94].

While trabeculectomy may not be an ideal option for patients with pre-existing ocular surface disease, minimally invasive glaucoma surgery (MIGS) with less potential interaction with the ocular surface [iStent (Glaukos Corp., Laguna Hills, CA), Hydrus Microstent (Ivantis Inc., Irvine, CA), CyPass Microstent (Alcon, Fort Worth, TX), XEN Gel Stent (Allergan Plc, Dublin, Ireland), or ab interno trabeculotomy with the trabectome or Kahook Dual Blade (New World Medical, Rancho Cucamonga, CA)] may be more appropriate options for patients with concomitant ocular surface disease and glaucoma[95–97]. No current studies specifically examining the effect of these new technologies on the ocular surface exist to our knowledge, but given that these surgeries spare the conjunctiva and decrease the burden of topical glaucoma drops, they may result in less irritation to the ocular surface.

Future Directions

Two new drops have recently been approved in the United States for topical treatment of glaucoma. Netarsidil 0.02% (Rhopressa, Aerie Pharmaceuticals, Irvine, CA), recently approved for topical use in the United States, is a Rho-kinase inhibitor and norepinephrine transporter inhibitor that lowers intraocular pressure and also causes conjunctival hyperemia in 50 to 53% of patients[98]. This hyperemia, graded by investigators on a scale of 1 to 4 at worsening severities at each follow-up, did not cause significant ocular symptoms and may be due to the ability of Rho-kinase inhibitors to cause vasodilation in vascular smooth muscle[98]. The second agent newly available for topical use is 0.024% latanaprostene bunod (Vyzulta, Bausch and Lomb, Bridgewater, NJ). Latanaprostene bunod is a nitric oxide donating prostaglandin F2 analog. Patients using 0.024% latanaprostene bunod for a mean of 90 days did have an increase in conjunctival hyperemia (5.9%), eye pain (3.9%), and eye irritation (4.2%) from baseline in comparison to 0.5% timolol[99].

While glaucoma is primarily treated with topical medications, introduction of new forms of drug delivery may revolutionize glaucoma care and also minimize ocular surface toxicity. Sustained release formulations allowing for a depot release of glaucoma medications that could last for weeks or months are currently in development. These include the bimatoprost ocular insert, latanoprost and travoprost punctal plugs, latanoprost-eluting contact lenses, bimatoprost and travoprost intraocular implants. Such formulations are applied in the subconjunctival space, inserted into the punctum, placed on the ocular surface, or injected intracamerally [100,101]. Travoprost punctal plugs are able to slowly release the prostaglandin analog into patients' tear film over a 90 day period and was found to not cause any hyperemia in a pharmaceutical phase 2b glaucoma clinical trial[101]. Notably, an early animal study using subconjunctival dorzolamide found post-injection subconjunctival inflammatory cells indicating that the subconjunctival application of these medications may still result in some clinical or subclinical ocular surface inflammation[102]. Further study is required to assess the potential benefit of decreased ocular surface toxicity with these new formulations.

Conclusion

The coexistence of glaucoma, glaucoma therapy, and ocular surface disease is an important consideration for patients and physicians. When prescribing medications, being conscious of potential ocular surface symptoms and patient risk factors for ocular surface disease may improve both patient and physician satisfaction with both current and new therapies. Further studies are needed to elucidate the complex relationship between these two ocular diseases. However, based on available literature, a variety of possible strategies reviewed here for reducing ocular morbidity from ocular surface disease in patients being treated for glaucoma can be employed while also improving adherence and success of glaucoma therapies.

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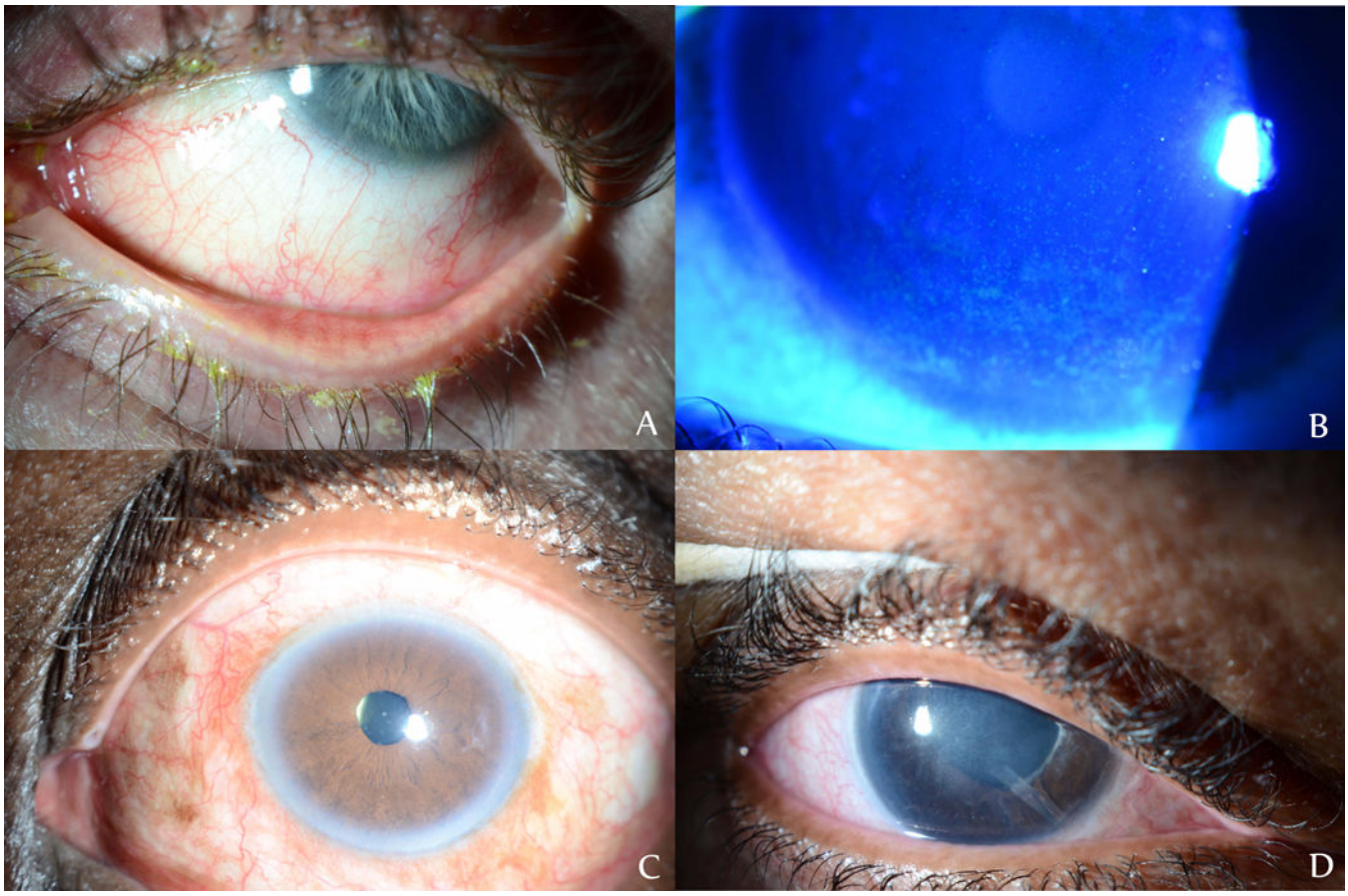

Figure 1.

Examples of ocular surface disease in glaucoma patients poorly-tolerant to topical antiglaucomatous drops A) Evidence of telangiectatic vessels at lid margin, matting of lashes, and meibomian gland disease after separate trials of brimonidine tartrate/timolol maleate 0.2%/0.5%, latanoprost 0.005%, bimatoprost 0.01%, timolol 0.5% B) Diffuse punctate epithelial erosions under fluorescein staining in a patient on bimatoprost 0.01%, brimonidine tartrate 0.1%. C) Diffuse conjunctival hyperemia in a patient on travoprost 0.004% D) Diffuse conjunctival injection and subepithelial haze from persistent epitheliopathy after taking multiple BAK-containing glaucoma drops, including brimonidine tartrate/timolol maleate 0.2%/0.5%

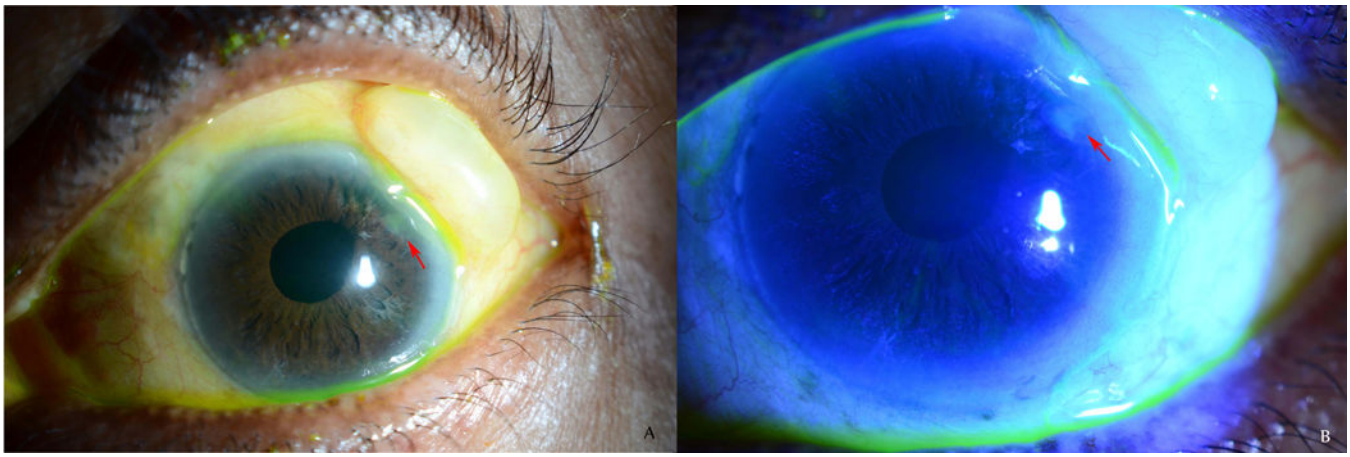

Figure 2.

Example of ocular surface disease in glaucoma patient resulting from glaucoma surgery and large bleb A) White light photograph B) Epithelial defect anterior to bleb is highlighted with fluorescein staining (see red arrows)

Table 1

Pertinent studies assessing ocular surface disease in anti-glaucomatous formations preserved with BAK

Reference	Type of Study	Patient Population	Medications being compared	Time frame of medication use	Results
Baudoin, 1998[39]	Crossover, randomized double blind study	30 healthy volunteers	Topical 2% carteolol with and without preservative	Short-term use (3 days)	TBUT was significantly reduced at 3 hours and after 3 days in the PF carteolol No difference in Schirmer's test, corneal aesthesiometry, IOP lowering effect, subjective tolerance
Henry, 2008[71]	Prospective, multicenter, historical control study	691 patients with ocular hypertension or primary open angle glaucoma	Switching from latanoprost or bimatoprost to travoprost BAK-free (Travatan Z, Alcon Laboratories, Inc., Fort Worth, TX, USA)	Intermediate-term use (3 months)	Mean OSDI scores were significantly improved, mean IOP was significantly decreased, conjunctival hyperemia significantly decreased in PF travoprost
Jaenen, 2007[12]	Multicenter cross-sectional epidemiologic survey in four European countries	9658 patients with open angle glaucoma	Preservative vs. PF beta-blocking drops	Varies	Pain or discomfort during instillation, foreign body sensation, stinging or burning, dry eye sensation significantly less frequent in PF group
Januleviciene, 2012[51]	Prospective, observer-masked study.	60 eyes of 30 open angle glaucoma patients	Switching from BAK-preserved latanoprost to PF tafluprost	Intermediate-term use (3 months)	Tear film osmolarity decreased significantly, mean TBUT increased significantly, abnormal fluorescein staining decreased significantly, subjective complaints decreased significantly in the PF group No statistically significant difference in IOP
Kanamoto, 2015[103]	Prospective, randomized, observer unmasked, multicenter crossover trial	174 glaucoma patients	Tafluprost with 0.001% BAK vs. travoprost with SofZia	Intermediate-term use (3 months)	Total superficial punctate keratopathy scores, conjunctival hyperemia scores were decreased in patients using SofZia-preserved travoprost No statistically significant difference in TBUT, IOP-lower effect, superficial punctate keratopathy scores of the superior/central/inferior areas.
Martone, 2009[29]	Retrospective, single-masked clinical study	84 patients with primary open-angle glaucoma or ocular hypertension and 20 health age-matched volunteers	Untreated vs. timolol with 0.01% BAK vs PF timolol vs latanoprost with 0.02% BAK vs. timolol/latanoprost combination drop with 0.02% BAK vs. timolol with 0.01% BAK and latanoprost with 0.02% BAK separately	Long-term use (23 to 28.7 months)	Patients on glaucoma drops statistically more significant ocular surface disease than untreated eyes. Corneal sensitivity, Schirmer I test, TBUT, superficial epithelial cell density were significantly lower in the preservative

Reference	Type of Study	Patient Population	Medications being compared	Time frame of medication use	Results
					medication groups compared to the preservative-free group Stromal keratocyte activation was higher in the preservative medication groups
Wong, 2018[104]	Cross-sectional, investigator-masked, paired-eye comparison study	33 patients with open angle glaucoma or ocular hypertension receiving medication in only one eye	88% of study participants used prostaglandin analogues. 100% used BAK-containing eye drops.	Intermediate to long-term use (at least 6 months)	Treated eyes had statistically significant poorer tear film osmolarity, decreased TBUT, decreased tear meniscus height, and increased eyelid margin abnormality scores. No statistically significant difference in meibomian dropout, expressed meibum content, ocular surface staining.
Yamazaki, 2010[70]	Prospective multicenter, open-label uncontrolled study	45 patients with open-angle glaucoma or ocular hypertension	Switching from BAK-preserved latanoprost to SofZia-preserved travoprost	Intermediate-term use (3 months)	Mean superficial punctate keratopathy score decreased significantly in the whole cornea after switching for SofZia-preserved travoprost