INTRODUCTION

Ocular surface disease refers to a complex grouping of non-specific symptoms, such as irritation, burning, foreign body sensation, dryness, and fluctuating vision [1], and signs, which mainly involve damage of the conjunctival and corneal surface, inadequate team film production, and increased team evaporation [2]. Symptoms of ocular surface disease adversely affects patients' quality of life [3] and can be severe and often debilitating: ocular surface symptoms are correlated with decreased ability to perform daily activities, ability to work, and emotional well-being [4]. While approximately 15% of the general elderly population experience some level of ocular surface disease [2], nearly 60% of patients with glaucoma report ocular surface symptoms [1, 5].

The most common initial treatment for glaucoma are topical anti-glaucoma medications, [5] which have been implicated as frequent causes of ocular surface disease. Patients on topical anti-glaucoma medications present with symptoms of ocular surface disease more often than a similar control group [3]. Furthermore, patients on topical anti-glaucoma medications for longer periods report more severe ocular surface symptoms than patients that are on these medications for shorter periods [2, 6, 7]. Additional evidence of the relationship between ocular surface disease and topical anti-glaucoma medications include the positive relationship between both the number of anti-glaucoma medications prescribed and number of instillations with the prevalence of ocular surface signs and symptoms [3, 8-10]. Surgical/procedural interventions can also cause ocular surface disease [11, 12], while the co-existence of ocular surface disease and glaucoma can also not be overlooked [5].

Addressing ocular surface disease in patients with glaucoma is important not only to improve patients' quality of life and ocular health but also to improve patients' adherence to treatment [13, 14]. In this article, we will review signs and symptoms of ocular surface disease, identify main causes of ocular surface disease in patients with glaucoma, and describe treatment and management options for addressing ocular surface disease in patients with glaucoma.

SIGNS OF OCULAR SURFACE DISEASE

Signs of ocular surface disease are commonly seen in patients with glaucoma and evaluated most frequently through slit lamp examination including vital dye staining of the cornea and conjunctiva, evaluation of meibomian gland function, determination of tear breakup time, and Schirmer's testing [9, 15]. The most common corneal finding associated with ocular surface disease is superficial punctate keratitis (SPK), which is seen in 18-31% of patients on anti-glaucoma medications [10, 16] and appreciated mainly through fluorescein instillation and examination with a cobalt blue light. Positive lissamine green staining on the bulbar conjunctiva is seen in 22% of patients on topical anti-glaucoma medications [1] and increased bulbar conjunctiva hyperemia has been reported in patients' eyes monocularly treated with topical anti-glaucoma medications compared to fellow untreated eyes [17]. Long-term use of topical anti-glaucoma medications also leads to meibomian gland dysfunction [15] and loss [9]. Specifically, in a study comparing meibomian gland dysfunction in 50 patients on topical anti-glaucoma medications with controls, 82% had meibomian gland dysfunction versus 52.5% in the control group [18]. Similar studies have found significantly worse meibum quality, thinner

lipid layer thickness, and lower meibomian gland secretion in patients with glaucoma compared to healthy controls [19, 20]. Such abnormalities in the lid margin can lead to tear film instability as assessed through a more rapid tear break-up time [1] and poorer non-invasive tear break-up time [17]. Tear film hyperosmolarity [9], reduced tear meniscus height [17], and lower Schirmer scores are also appreciated in patients on topical anti-glaucoma medications [1].

SYMPTOMS OF OCULAR SURFACE DISEASE

Common symptoms of ocular surface disease include dryness, redness, irritation, burning, foreign body sensation, photophobia, and distorted vision [1, 21, 22]. Such symptoms can be seen in patients on topical anti-glaucoma medications within 3 months of medication initiation (Ramli et al., 2015). One of the most common tools to evaluate and quantify these symptoms is the Ocular Surface Disease Index (OSDI). The OSDI is a 12-item functional questionnaire with a diagnostic cut-off of greater than or equal to 13. Higher OSDI scores are generally associated with worsening ocular surface symptoms [15, 23, 24]. Higher OSDI scores have also been related to more severe symptoms of glaucoma based on the Glaucoma Quality of Life-15 (GQL-15), which is a 15-item questionnaire created to estimate the impact of glaucoma on daily visual function [23]. It is important to note that ocular surface disease and glaucoma can both adversely affect visual function and quality of life [3].

CAUSES OF OCULAR SURFACE DISEASE IN PATIENTS WITH GLAUCOMA

Ocular surface disease in patients with glaucoma is often related to the use of topical anti-glaucoma medications, whether related to the preservative, active ingredient, or both; it can also be due to surgical/procedural interventions and may also co-exist independently.

RELATED TO PRESERVATIVES IN TOPICAL ANTI-GLAUCOMA MEDICATIONS

Benzalkonium chloride (BAK), the most widely-used preservative in ophthalmic medications including anti-glaucoma medications, is a broad-spectrum antimicrobial detergent that causes cell wall and cytoplastic membrane [25]. As a cationic quaternary ammonium structure, BAK also promotes drug transmission into the anterior chamber by acting as a surfactant [26]. These properties interfere with the lipid layer of the tear film, resulting in shorter tear film breakup time and increased aqueous tear evaporation [16, 27]. Lower Schirmer values have also been reported in patients receiving BAK-preserved timolol compared to controls [28]. Benzalkonium chloride has also been implicated in the reduced density of goblet cells [5], impaired mucin production [29], greater amount of squamous epithelial cell metaplasia [30], decreased corneal stromal nerve fiber density [31], shorter survival of corneal endothelial cell [32], and reduced corneal sensitivity [33] compared with healthy age-matched controls. Use of BAK has also been associated with increased conjunctival hyperemia, subconjunctival fibrosis, epithelial apoptosis [34], and release of matrix metalloproteinase- 9 by trabecular meshwork cells [35]. Time and dose-dependent toxicity of BAK on the conjunctiva and corneal epithelium have been reported [34, 36]. In addition to ocular signs of inflammation related to BAK, patients on topical anti-glaucoma medications with BAK also report Increased pain during drop instillation, foreign body sensation, burning, and dry eye sensation compared to those on the preservative-free equivalent [16].

RELATED TO ACTIVE INGREDIENTS IN TOPICAL ANTI-GLAUCOMA MEDICATIONS

There is evidence suggesting that ocular surface disease can be directly related to the active pharmaceutical agents in topical anti-glaucoma medications [15]. While particular caution has been advised in prescribing topical beta-blockers [15], ocular surface disease has also been described as being due to topical prostaglandin analogs and alpha adrenergic agonists [37]. Beta-blockers such as timolol have been reported to act on beta receptors in the lacrimal gland in reducing basal tear turnover rate [38]. Timolol has been found to alter the mucus composition in the tear film, cause increased staining of the cornea and conjunctiva [39], and a dose-dependent decrease in the survival of immortalized human meibomian gland epithelial cells has been described [40]. An association with both a higher prevalence and severity of obstructive meibomian gland dysfunction with prostaglandin analogs has also been reported [41], while brimonidine, an alpha-adrenergic agonist, has been seen to cause a dose-dependent decrease in the proliferation of immortalized human meibomian gland epithelial cells [42]. High rates of ocular allergy have also been reported in patients treated with brimonidine [43].

OTHER CAUSES OF OCULAR SURFACE DISEASE IN PATIENTS WITH GLAUCOMA

Post-operative structural alterations can cause changes to the ocular surface and lead to the initiation or exacerbation of ocular surface disease. Specifically, patients undergoing trabeculectomy had a higher rate of ocular irritation at five years [11]. Ocular surface disease following the use of medications such as mitomycin C and 5-fluorouracil, as well as anatomic problems such as bleb dysthesia [12] have also been reported.

It is important to recognize that ocular surface disease and glaucoma can both overlap and co-exist independently since both glaucoma and ocular surface disease are positively correlated with patient age. Older patients are more likely to have both glaucoma and ocular surface disease [44], have had the disease(s) longer, undergone more treatment, and/or have more severe forms of the disease(s) [45]. Despite this relationship, it is important for eye care providers to recognize the impact that interventions to treat and manage glaucoma can have on the ocular surface and address such concerns and thus reduce further ocular morbidity and to improve the success of glaucoma therapy.

TREATMENT AND MANAGEMENT OPTIONS FOR ADDRESSING OCULAR SURFACE DISEASE IN PATIENTS WITH GLAUCOMA

Initial management of ocular surface disease in patients with glaucoma can include more traditional methods of managing ocular surface disease, such as the initiation of artificial tears [46] or topical cyclosporine [47]. It may be more appropriate, however, to address the fundamental cause of the ocular surface disease, which is, for many of these patients, caused by a reaction to BAK. In these cases, eliminating exposure to BAK by moving to newer BAK-free alternatives, switching to preservative-free topical anti-glaucoma medications, and considering surgical/procedural interventions that do not cause damage to the conjunctiva and cornea are also appropriate options. The latter two options also address reactions that patients may have to the active ingredients in topical anti-glaucoma medications. Minimizing exposure to BAK by switching from multiple agents with BAK to combination medications or changing to a different

topical anti-glaucoma BAK-containing medication with a more optimized dosing schedule may be sufficient for patients where BAK is the cause of their ocular surface disease.

USING MORE TRADITIONAL METHODS OF MANAGING OCULAR SURFACE DISEASE

Patients on topical anti-glaucoma medications who used artificial tears containing 0.18% sodium hyaluronate showed significantly more improvement in both signs, such as reduced lid margin inflammation and conjunctival injection and increased goblet cell density and tear break-up time [48-50]. Prabhasawat and colleagues [51] identified corresponding improvements in symptoms of ocular surface disease, as identified through decreased OSDI scores, in glaucoma medications using artificial tears. Improved visual field parameters in patients using artificial tears [52] has also been reported. Topical cyclosporine 0.05% has been found to be beneficial for ocular surface disease in patients with glaucoma, both those on topical anti-glaucoma medications [47] and after a trabeculectomy [23]. Avoiding use of punctal occlusion is recommended in these patients since this retains and increases absorption of the anti-glaucoma drug and preservatives like BAK [12], both of which can be causes of these patients' ocular surface disease.

ELIMINATING EXPOSURE TO BAK

Clinical benefits of addressing ocular surface disease in BAK-sensitive patients with glaucoma have been demonstrated in patients that are switched to newer BAK-free alternatives [5, 9]. These alternatives include:

- Polyquarternium-1 (Polyquad, Alcon Laboratories, Fort Worth, TX), which is a quaternary ammonium preservative [9] that induces less ocular surface damage [53, 54] and is associated with significantly higher level of visual comfort and function compared with patients using BAK preserved travoprost [55]. Polyquad is used in Travatan Z formulations outside of the United States (Alcon Laboratories, Fort Worth, TX).
- SofZia preservative system (Alcon Laboratories, Fort Worth, TX), which is an ionic buffer solution that converts to non-toxic by-products after coming into contact with ocular surface cations [9]. Studies have demonstrated decreased conjunctival hyperemia, greater corneal and conjunctival cell survival, improved tear break-up time, reduced OSDI scores, and improved visual acuity [53, 56-58]. SofZia is used in Travatan Z (Alcon Laboratories, Fort Worth, TX).
- Stabilized oxy-chloro complex (Purite, Bio-Cide International Inc., OK) has been found to have a mild incidence of adverse effects such as conjunctival hyperemia [15] and is used in Alphagan P (Allergan, Irvine, CA).

Switching to preservative-free topical anti-glaucoma medications, such as Cosopt preservative free and timolol preservative free in single-dose packaging, is also an option. However, it is important to keep in mind:

- Access, since glaucoma medications with non-BAK preservatives and preservative-free topical medications are not always available in all countries,
- Cost differences, because preservative-free alternatives are usually more expensive, and
- Contamination concerns, keeping in mind that preservatives kill pathogens that can cause significant ocular harm

Surgeries/procedures that do not cause damage to the conjunctiva and the cornea and allow patients to avoid or decrease their reliance on topical anti-glaucoma medications that can cause ocular surface disease are also appropriate options. Specifically, laser trabeculoplasty, minimally invasive glaucoma surgeries, and novel forms of drug delivery may result in improved outcomes for both ocular surface disease and glaucoma. It is important to note that ocular surface disease has been linked to a higher rate of failure in sub-conjunctival glaucoma surgery [59, 60], so addressing ocular surface disease prior to glaucoma surgery is prudent.

MINIMIZING EXPOSURE TO BAK

Given that eliminating exposure to BAK may not be possible, minimizing exposure may be sufficient and achieved by switching patients on multiple agents with BAK to combination medications to decrease the overall BAK exposure amount [12]. Switching to a BAK-containing topical anti-glaucoma medication with a more optimized dosing schedule, such as a once-nightly prostaglandin analog, is also appropriate.

CONCLUSION

When faced with the need to treat a potentially blinding disease like glaucoma, concerns related to ocular surface disease may become secondary. However, ocular surface disease is more prevalent and more severe in patients with glaucoma, can significantly impact patients' quality of life, and be directly related to our efforts to treat and manage glaucoma. Eye care providers should regularly evaluate patients with glaucoma for signs and symptoms of ocular surface disease to ensure timely detection and initiation of treatment.

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