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Strategies for the Management of Ocular Surface Disease in Glaucoma

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INTRODUCTION:
Ocular surface disease (OSD) is a common ophthalmological concern, with a prevalence in the Canadian population estimated at 25%[1]. Amongst glaucoma patients, up to 60% report symptoms of OSD and up to 78% have clinical signs[2]. Surface symptoms significantly reduce glaucoma-related quality-of-life (QOL), and there is emerging evidence to suggest that treatment of OSD may in fact improve intraocular-pressure (IOP) control and contribute to disease stabilization[3,4]. The treatment of OSD in glaucoma has been receiving increasing attention, however specific recommendations remain sparse[5].

Ocular surface disease is known to represent a complex milieu of genetic predisposition, adnexal and periorbital status, environmental factors, systemic diseases, and medications (topical and systemic), amongst other predisposing factors. Effective management of this condition therefore demands that treatment be targeted to the specific clinical context. A 2020 study of Canadian glaucoma specialists found that, although 97% identified optimization of ocular surface disease as important for improving patient QOL, only 22.2% felt this was currently being managed adequately in the subspecialty clinic setting. Moreover, although all participants felt comfortable modifying topical hypotensive regimens to improve surface disease, only 61.1% were confident identifying patients who would benefit from topical steroids, and just 30.5% felt knowledgeable regarding the use and dispensation of autologous serum tears, which are increasingly deployed for treatment-resistant OSD in dry-eye practices[5]. There is, therefore, an unmet need for clarity in the treatment algorithm to optimize OSD in glaucoma patients. Here, we discuss the therapeutic approach to these patients and present a suggested algorithm to guide management.

STANDARDIZED SCORES/ASSESSMENT FORMS
There are many standardized assessment forms and criteria to grade the presence and severity of OSD in diverse populations, but these are currently underutilized in the glaucoma practice[5]. Amongst the most well-known is the Ocular Surface Disease Index (OSDI), but others—such as the Symptom Assessment in Dry Eye (SANDE), and Dry Eye Questionnaire-5 (DEQ-5)—all serve to quantify dry eye signs and symptoms in the clinical setting[6-9]. The chief benefits of these tools are providing consistent, reproducible means to assess disease activity which can be helpful in guiding therapy and gauging response to treatment in a quantifiable manner.

OPTIMIZATION OF ENVIRONMENTAL/PERIORBITAL FACTORS
The ocular surface is influenced by both local environmental and periorbital factors. An ambient humidity of 40-45% has been proposed as a reasonable target, as it has been shown that when humidity falls to 20-25%, evaporative tear loss increases by 99.7%[10].

Lid malposition such as entropion, ectropion, or lagophthalmos, and inflammatory lid disorders (such as blepharitis or rosacea) should be managed carefully in this population. Patients should also be examined for signs of predisposing conditions such as allergic conjunctivitis and contact-lens overwear, which should be managed aggressively.

STEPWISE TREATMENT ALGORITHM

The benefits of a stepwise approach to the management of surface disease include logical progression of care while minimizing both the cost and complexity of treatment. Such an algorithm is outlined below and presented in **Figure 1**. The use of a standardized approach eases clinical integration for the physician, reducing barriers for the initiation of the appropriate treatments, while offering the opportunity to 'step up' or 'step down' therapy based on a patient's symptoms, severity scores, and the tolerability of each treatment.

OPTIMIZATION OF GLAUCOMA THERAPY

It has been well-established that benzalkonium chloride (BAK)--one of the most common ophthalmic preparation preservatives--contributes to aqueous tear deficiency, evaporative tear film loss, and diminished reflex tearing, via decreased corneal sensitivity[11]. Further, there is data to suggest that chronic BAK exposure increases trabeculectomy failure rates[12] and active ingredients themselves impact many anterior segment structures[11]. Every effort should be taken, therefore, to minimize these effects. Various fixed-dose combination drops are available and reduce BAK exposure when compared to multi-drop regimens. Further, there are increasing options for alternatively-preserved or non-preserved formulations, which have fewer surface sequelae than BAK. Where possible, these should be employed, taking into consideration price and convenience factors for each patient.

Early intervention with laser trabeculoplasty as a drop-sparing therapy should be considered for glaucoma patients with OSD. Selective laser trabeculoplasty has been shown in large trials and meta-analyses to be equivalent to topical hypotensive agents as a first-line intraocular pressure (IOP)-lowering therapy, with further advantages in terms of cost-effectiveness and compliance[13]. Minimally invasive glaucoma surgery (MIGS) should be considered at the time of cataract surgery when appropriate to further reduce medication and preservative burden when clinically appropriate. *Ab interno*, conjunctiva-sparing MIGS may be favored, such as gonio-assisted trabeculotomy (GATT), Trabectome, iStent or Hydrus microstent.

While allergy is possible with any topical glaucoma formulation, which may include sensitivity to the active ingredient, preservative, or vehicle, alpha agonists such as apraclonidine and brimonidine have the highest incidence of allergic response. When considering allergic conjunctivitis or contact dermatitis, up to 25.7% of patients on brimonidine may develop a response[14]. If allergy is suspected to a topical formulation, consideration could be given to switching to another class of medication if appropriate, to another topical formulation within the same class of topical active ingredient, or to the same medication with an alternative or unpreserved formulation, if preservative sensitivity is suspected.

Step 1: Promote Ocular Surface Health

The ocular surface should be optimized with drops, punctal occlusion, and supplements. Mainstay therapy consists of artificial tears and ointments, with preference for non-preserved agents where possible. Dosing can be initiated with a frequency between QID and Q1H based on the severity of signs and symptoms. A viscous tear ointment/gel should also be considered for QHS usage, or indeed can be utilized more frequently during the day, however this may be limited by the patient's ability to tolerate the transient blurred vision that these agents often induce.

Punctal occlusion has been shown to decrease standardized OSD severity scores[4], with many options available. Absorbable plugs may allow for a temporary trial

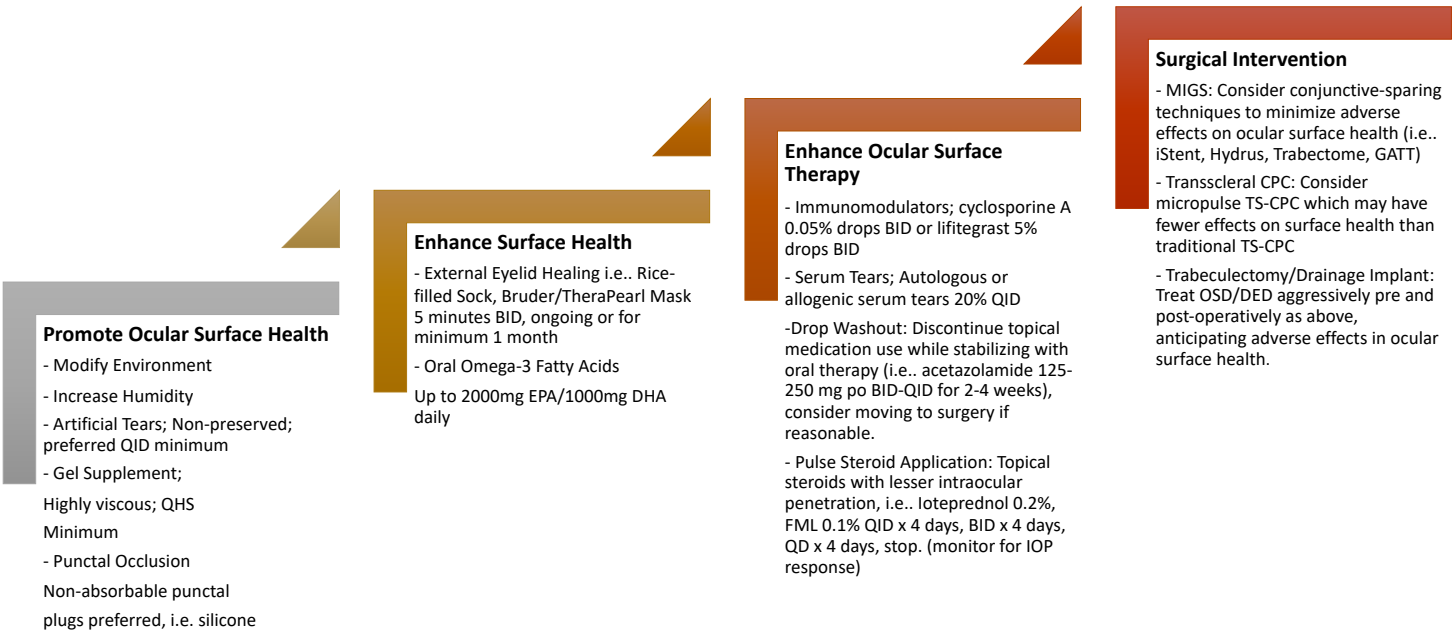

Figure 1. Stepwise approach to ocular surface disease management in glaucoma patients; adapted from Muzychuk et al, 2020

EPA: eicosapentaenoic acid; **DHA:** docosahexaenoic acid; **IOP:** intraocular pressure; **MIGS:** minimally invasive glaucoma surgery ; **GATT:** Gonioscopy-assisted transluminal trabeculotomy; **CPC:** cyclophotocoagulation; **OSD:** ocular surface disease; **DED:** dry eye disease

of punctal occlusion with an absorbable plug and movement to permanent silicone plugging if successful, with punctal ablation available in cases of recurrent extrusion or plug discomfort. As permanent plugs may be more efficacious than temporary plugs, with specific evidence for their use in glaucoma, they may represent a reasonable starting point for punctal occlusion therapy, and moreover are typically reversible[4]. As increasing drop burden is known to impact compliance, punctal occlusion may be particularly compelling for patients already on complex drop regimens. If there is a paradoxical worsening in OSD signs and symptoms, these should be removed as it is theoretically possible that patients with inflammatory dry eye may worsen due to pooling of inflammatory mediators.

External eyelid heating devices are effective in reducing surface staining and improving tear breakup time (TBUT) and meibomian gland secretion quality[15]. Optimally, patients are advised to use BID-TID applications of these devices in a minimum of 5 minute increments. Due to evaporative cooling associated with wet devices, commercially available dry heating devices are preferred.

Omega-3 supplementation has been widely investigated as an OSD therapy. One of the largest randomized-controlled trials, the NIH-funded DREAM study, showed no benefit over placebo[16] while a subsequent large-scale meta-analysis found omega-3 significantly improved OSD symptoms/signs[17]. Doses up to 2000 mg of eicosapentaenoic acid and 1000 mg of docosahexaenoic acid daily were well tolerated. Though possibly of modest effect, omega-3 may be considered for patients with treatment-resistant OSD.

Step 2: Enhance Ocular Surface Health

For refractory disease, escalation of therapy with immune-modulators and serum tears may be necessary. A recent prospective study demonstrated that six months of topical cyclosporine A 0.05% significantly improved TBUT, corneal staining, and OSDI scores in patients on BAK-preserved glaucoma drops[18]. In Canada, topical cyclosporine 0.09% and 0.1% are also commercially available. Lifitegrast 5% modulates T-cell activity implicated in the pathogenesis of OSD, and although yet to be studied in glaucoma, may hold promise for these patients.

Autologous serum tears may also be considered for recalcitrant OSD in this clinical setting. These have been shown to contain growth factors, fibronectin, and vitamin A—integral components in the tear film and surface signaling. These are typically initiated at a concentration of 20% QID-Q2H, and superiority over artificial tears in the setting of severe OSD has been demonstrated[19]. Higher concentrations (30% and 40%) can also be compounded but the excess protein concentration can make the solution thicker which some patients may not prefer. Cost and compounding access limit their use however; allogenic serum tears derived from donor blood products may mitigate these constraints.

Step 3: Enhance Ocular Surface Therapy

When the above steps prove inadequate, topical glaucoma therapy washout should be considered, provided the patient can be maintained on oral agents (such as acetazolamide) alone for a 2-4 week period. This may be performed independently or combined with a short course of topical corticosteroid to interrupt the cycle of surface inflammation. Topical corticosteroids used preoperatively for trabeculectomy have been shown to improve outcomes; it is hypothesized that this occurs by reversing medication-induced conjunctival inflammation, but specific recommendations for their use in glaucoma therapy-induced OSD are lacking[20]. Care should be taken to minimize steroid response when selecting an agent, and careful monitoring of IOPs should be undertaken for the duration of therapy. Preparations such as fluorometholone or loteprednol etabonate may have lesser IOP-raising effects; reasonable choices include fluorometholone 0.1%, loteprednol etabonate 0.2-0.5%, or prednisolone 0.5%. A short course may comprise an initial application QID, reducing the dosage by half every 4-7 days until completion.

Step 4: Surgical Intervention

Finally, if the outlined steps are unsuccessful, drop-sparing surgical intervention may be considered. Ab interno, conjunctiva-sparing MIGS procedures may be favored, such as GATT, Trabectome, iStent, or Hydrus microstent. While the Xen gel implant forms a filtering conjunctival bleb and is often used in conjunction with mitomycin C (MMC), it can obviate the need for conjunctival dissection, which may in theory better preserve ocular surface health. Micropulse cyclophotocoagulation, when appropriate for the targeted IOP reduction, may have fewer adverse effects on the ocular surface than traditional continuous wave due to its “on-and-off” cycle, allowing structures adjacent to the targeted pigmented ciliary epithelium to cool, protecting them from collateral thermal damage[21]. Trabeculectomies and glaucoma drainage devices remain the mainstay for cases necessitating significant IOP reduction, however. In any bleb-forming procedure, the possible implications of the bleb itself for ocular surface health must be considered. Blebs are known to interfere with proper lid function, compromise the precorneal tear film, and elevated/cystic blebs have been implicated in worsening OSD[22]. Further, MMC—a common adjunct in modern filtering procedures—is known to have adverse effects on limbal stem cells and decreases conjunctival goblet cell density[23]. Therefore, it is advisable to optimize all other factors for the ocular surface prior to surgery, anticipating its potential adverse effects on surface health.

ADDITIONAL MODALITIES

Newer therapeutic modalities may be considered on an individualized basis. Among the most studied of these modalities in ocular surface disease are intense pulsed light (IPL) and thermal pulsation (i.e.. LipiFlow, Johnson & Johnson Vision, Jacksonville, FL, USA; iLux, Alcon Laboratories), particularly in the setting of significant meibomian gland disease (MGD). A cross-sectional study found MGD to be present in 80% of patients with glaucoma on topical IOP-lowering agents, however, the presence of MGD did not appear to have an additional detrimental

effect on the ocular surface to those induced by topical glaucoma medication use[24]. In glaucoma patients with OSD, a small, non-comparative series on IPL demonstrated significant improvement in signs and symptoms of OSD[25]. However, a randomized controlled trial evaluating thermal pulsation with lid hygiene versus lid hygiene alone for glaucoma patients with OSD failed to demonstrate an added benefit with thermal pulsation over lid hygiene measures alone[26]. Future studies may better delineate the role for these newer modalities for the treatment of OSD in glaucoma. As with all interventions, cost and availability must be carefully considered.

CONCLUSION

The management of ocular surface disease in glaucoma is multifaceted but may be streamlined through the adoption of a stepwise algorithm. By treating aggravating comorbidities, optimizing the patient's topical glaucoma and dry eye therapy, and considering drop-sparing laser and surgical therapies using techniques that may be less likely to worsen ocular surface disease, physicians may be better able to address this frequently comorbid condition.

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