Chapter

Dry Eye and Allergic Conjunctivitis

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Abstract

The primary goal of this chapter is to discuss the nuanced but prevalent clinical presentation of the patient with concurrent diagnoses of dry eye and allergic conjunctivitis. First, we discuss the epidemiology of dry eye disease and allergic conjunctivitis. We briefly discuss allergic blepharoconjunctivitis, a closely related entity with a different treatment focus. We thereafter discuss novel therapies, including loteprednol, varenicline nasal spray, reproxalap, and drug-eluting daily disposable soft contact lens. Lastly, we discuss a few biologic agents that hold promise for vernal and atopic keratoconjunctivitis, two forms of allergic eye disease that are more aggressive and can result in severe vision loss.

Keywords: tear film instability, ocular toxicity, allergic conjunctivitis, dry eye, allergic blepharoconjunctivitis

1. Introduction

Dry eye disease is a ubiquitous and often chronic condition, encountered frequently in ophthalmic practice. In 2017, more than 16 million Americans were afflicted by dry eye, approximately 6.8% of Americans [1]. Twice as common in women as in men, dry eye has also been demonstrated to increase in frequency with advancing age. With an aging population, the prevalence of dry eye will only increase. Typical symptoms of dry eye often include eye pain, grittiness, photophobia and blurred vision. The definition of dry eye disease was recently refined by the Tear Film & Ocular Surface Society International Dry Eye Workshop II (TFOS DEWS II) as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [2]. It should come as no surprise that additional ocular pathology, including meibomian gland dysfunction, allergic eye disease and iatrogenic factors, such as cataract surgery, can exacerbate dry eye by disrupting homeostasis of the tear film.

A variety of inflammatory ocular surface conditions can result in increased tear film osmolality and disruption of tear film homeostasis. Allergic conjunctivitis is classically associated with IgE-hypersensitivity to allergens. Within this cascade involves activation of mast cells, which results in an early response and a late phase response. The early response is associated with elevated levels of prostaglandins and histamine within the tear film [3]. The late response involves upregulation of interleukin-8 (IL-8) and macrophage inflammatory protein (MIP) [3]. Frequently, this presents

clinically as tear film instability with inflamed conjunctival mucosa. In this chapter, we will focus on allergic eye disease as a concomitant diagnosis complicating the management of dry eye, in addition to highlighting novel treatments that are promising for the management of both conditions.

Allergy is a widespread condition, but ocular manifestations of allergic disease may be under-recognized within our current population. The first attempt at providing epidemiology on the incidence of specifically allergic eye disease was through data obtained between 1988 and 1994 [4]. While allergic rhinitis had previously been evaluated on prior censuses, allergic ocular symptoms had been overlooked. In this first evaluation, almost 30% of people had both nasal and ocular symptoms, with far fewer reporting ocular symptoms alone (6.4%). This study also revealed that isolated ocular symptoms are more common in patients as they age, typically over 50 years old, compared to combined nasal and ocular symptoms in younger age groups [4]. This should come as no surprise as it has already been thoroughly documented that the prevalence of atopy decreases with age whereas the prevalence of dry eye increases with age.

Like many diseases, allergic eye disease exists on a spectrum, with milder forms of allergy including seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), ranging to the more severe atopic (AKC) or vernal keratoconjunctivitis (VKC). Whereas SAC and PAC classically impact the conjunctiva, VKC more frequently impacts the cornea and can severely reduce visual acuity through shield ulcers, vernal plaques and neovascularized scars [5]. As such, the treatments for allergic eye disease can vary widely in intensity depending on the severity of the presentation. VKC is more common among patients with concomitant atopic disease; as such, the more severe forms of ocular allergy are more likely to affect younger patients. Particularly for younger patients who may still be within the amblyogenic age range, aggressive management is indicated to combat corneal manifestations of VKC, in some cases requiring systemic therapies. For SAC and PAC, management is more often through topical therapies, but can become difficult when faced with coexistent dry eye.

In most studies related to ocular allergens, the predominant focus is most often on SAC and PAC as these are conditions more prevalent in older age groups, and thus within the work force. There are several well-documented allergens that are more likely to present with ocular symptoms as opposed to nasal symptoms: pet dander, dust, pollen, mold, and certain cosmetics. An additional interesting feature of this study was that the allergic disease was more prevalent in the southern United States, presumably secondary to higher humidity and relatively more pollen production [6]. With ongoing climate change and global warming, pollen production will continue to increase, suggesting that the prevalence of ocular allergy will only increase with time. Another consideration regarding ocular allergy prevalence includes the impact on vision, quality of life and economic productivity. While only 3% of adults have symptoms severe enough to prevent working outside of the home, the AIRS Survey revealed that the average self-reported decrease in productivity from allergic eye disease was 26 points, falling from a self-reported productivity of 91/100 with no allergic symptoms to 65/100 with the worst allergic symptoms [7]. As such, there is a need for effective therapies to mitigate the symptoms of allergic eye disease, to improve quality of life for those suffering from allergies and to enable these patients to continue to engage fully in their professions, instead of being limited by their symptoms.

Classic symptoms of allergic eye disease often overlap with those of dry eye, including redness, itching/pruritis, grittiness, burning, epiphora/tearing and blurred

vision. However, allergic eye disease complicates the management of dry eye, as some treatments for stand-alone dry eye may not be as effective or as tolerable for the patient with concomitant allergic disease. Artificial tears may be considered as an initial therapy for patients with either dry eye or allergic conjunctivitis, but further treatment choices may become more difficult. It is not uncommon for muscarinic topical anti-histamines to dry the ocular surface, while topical therapies for dry eye and meibomitis frequently create hypersensitivity or irritative effects on the allergic ocular surface. Similarly, punctal plugs obviously would be a less desirable choice in a patient with allergic conjunctivitis, as this would result in prolonged exposure of the allergen to the ocular surface. Mast-cell stabilizers may be of utility in these patients, but can take days to weeks to reach peak efficacy, and as such, will not provide patients with immediate relief. As such, there is a need for more nuanced medications that can adequately address both allergic conjunctivitis and dry eye.

2. Allergic contact blepharoconjunctivitis

First, we will briefly discuss allergic contact blepharoconjunctivitis, a disease similar to SAC and PAC, but with slightly different management. The most common cause of an allergic contact blepharoconjunctivitis is the use of cosmetics. The inciting agent in these cases can include a variety of metal allergies, such as nickel, cobalt and chrome, as well as allergies to the fragrances added to these cosmetics [8]. While the solution for blepharoconjunctivitis in the setting of cosmetic use may be simple, allergen avoidance, it can often be difficult to pinpoint a cosmetic as the underlying cause of symptoms. Often, the history may be challenging. Women, who are twice as likely as men to experience symptoms of dry eye, are more likely to wear cosmetics, specifically mascara, on a daily basis. As such, their constellations of symptoms could easily be confused with an environmental allergen (akin to dust or dander). Furthermore, this allergic blepharoconjunctivitis may be exacerbated by the mechanical impact of cosmetic products. For example, application of mascara or eyeliner may obstruct meibomian gland orifices, which can lead to further team film instability and aggravation of dry eye and allergic symptoms [8]. As previously mentioned, dry eye is twice as common in women as in men, so providers must be aware of the impact of cosmetic use. For patients in whom allergen avoidance is less practical, such as those suffering from pollen allergies, there are a variety of novel therapies being released to attempt to better control the nuanced symptoms of concomitant dry eye and allergic eye disease.

3. Novel treatments for seasonal and perennial allergic conjunctivitis

One of the first efforts to address the inflammatory component of dry eye was the application of topical steroid therapy. In late 2020, KPI-121 0.25% (EYSUVIS, Kala Pharmaceuticals, Inc.) became the first commercially available mucus-penetrating particle (MPP) formulation of loteprednol etabonate ophthalmic emulsion approved for episodic dry eye. Investigated through the STRIDE trials, loteprednol etabonate was approved for four times daily (QID) use up to 2 weeks at a time [9, 10]. The mucus-penetrating particle vehicle enables the medication to avoid entrapment by conjunctival mucins and achieve better ocular penetration [9, 10]. For patients with a component of allergic disease, a low-dose topical steroid may be of particular use,

as an intermittent topical steroid therapy may address underlying inflammation present in both dry eye and allergic disease. There are however some patients for whom a topical steroid may not be the best treatment option. For example, while there were no differences in intraocular pressure between the two STRIDE trial arms, loteprednol still has a higher rate of elevated intraocular pressure (IOP) than other topical medications such as olopatadine. As such, practitioners may still be hesitant to prescribe loteprednol for the patient with glaucoma, who may have a higher proclivity of IOP elevations [10]. Furthermore, as the medication is approved for only 2 weeks at a time, loteprednol would not be the best first choice for a patient with perennial symptoms.

Another medication that may be of particular interest for patients with both dry eye and allergy is Tyrvaya™ (varenicline solution) Nasal Spray. This novel dry eye treatment, initially approved in late 2021, enables a patient to avoid eye drops entirely. For some patients with either dry eye and/or allergic disease, application site reaction (i.e. burning pain on instillation of drops) may prohibit use of topical therapy. Tyrvaya™ could be considered in such patients, as the nasal spray circumvents this specific problem. Investigated by Ocean Point through the MYSTIC phase II randomized trial and the ONSET-2 Phase III Randomized Trial, Tyrvaya™ has repeatedly been shown to significantly improve signs and symptoms of dry eye [11, 12]. The primary endpoint in these studies was improvement in Schirmer's test by 10 mm or more by 4 out of 12 weeks of therapy; however, tear production was shown to increase as quickly as 5 minutes after administration [11]. While the exact mechanism of action is not completely understood, Tyrvaya™ is thought to be a neuro-stimulating agent, activating the parasympathetic pathway of the nasociliary branch of the trigeminal nerve in the nose, thereby increasing baseline tear production. Varenicline, the active ingredient in Tryvaya™, has previously been used as a smoking cessation aid. There is longstanding safety data for this medication, considering Chantix is used systemically in much higher doses with excellent tolerance. The side effect profile of Tyrvaya™ is relatively benign. The most common adverse reaction is sneezing, which occurs in 82% of patients. Cough, throat irritation and instillation-site (i.e. nose) irritation are among other common adverse reactions [11, 12].

While the use of Tryvaya™ in the setting of stand-alone allergic eye disease has not yet been investigated, for patients that suffer from both allergic eye disease and dry eye, Tryvaya™ may be of utility. Patients with a diagnosis of allergic rhinitis often use other medications administered via nasal spray to control their nasal symptoms, such as fluticasone, or FLONASE. For these patients, a nasal route of administration may be more-readily accepted, as they are familiar with/accustomed to this route of therapy. Given twice daily in each nostril, Tyrvaya™ can not only reduce topical treatment burden for patients, but is also an excellent option for patients who have difficulty with drops. Tyrvaya™ has advantages for patients with reduced neck mobility or reduced upper limb mobility, tremors, digital arthritis, patients who live alone and those who struggle self-administering eye drops. Another patient population that may benefit from Tyrvaya™ includes be the complex glaucoma patient who has developed allergic disease and toxicity in the form of medicamentosa. Of note, Tyrvaya™ has not been tested on patients with obstructive sleep apnea (OSA) who use continuous positive airway pressure (CPAP), with prior sinus surgeries, with a history of PKP, or those with recurrent nosebleeds [11]. As such, conclusions are unable to be drawn about its effectiveness in these specific demographics. Nevertheless, a single

pharmaceutical with both a new delivery route and a novel mechanism of action holds great potential for patients afflicted by dry eye and allergic eye disease.

Another novel therapeutic, Reproxalap, is currently being investigated and developed by Aldyera to address both allergic conjunctivitis and dry eye disease. This topical medication is a novel, small-molecule immune-modulating covalent inhibitor of reactive aldehyde species (RASP) [13, 14]. While the exact mechanism of action of Reproxalap is not completely understood at this time, it is hypothesized to address the inflammatory component of both dry eye and allergic disease. RASP potentiate inflammation through a variety of inflammatory mediators and pathways, and as such, inhibition of RASP may inhibit the propagation of the inflammatory cascades.

Reproxalap was first evaluated in the treatment of dry eye alone in the Phase III TRANQUILITY trial. Participants were randomized to 0.1% reproxalap, 0.25% reproxalap and placebo groups. They were then exposed to a controlled adverse environment, consisting of low humidity for 90 minutes, after a 12-week course of QID treatment. Symptomatic relief was appreciated as early as 2 weeks into the treatment course, at the first follow up visit [13]. Patients experienced symptomatic improvement in a dose dependent response, particularly in relation to symptoms of grittiness and dryness [13]. Researchers also appreciated improvements in nasal fluorescein staining in the 0.25% group, so 0.25% Reproxalap QID was advanced to additional clinical trials. For patients with allergic conjunctivitis, Reproxalap was evaluated in a randomized, double-blind Phase IIb Trial and in the Phase III ALLEVIATE Trial [14, 15]. In each of these studies, participants were randomized to various treatment groups, including 0.25% Reproxalap, 0.5% Reproxalap and placebo. For both doses, participants who had been administered Reproxalap noted improvement in symptoms, notably tearing, itching and redness [14, 15]. However, participants taking the higher dose, 0.5% Reproxalap, experienced a higher rate of instillation site reaction, with higher rates of redness and irritation after the first dose, so the 0.25% regimen is being advanced [14]. Reproxalap is a promising medication for those suffering from both dry eye and allergic conjunctivitis.

Another novel therapeutic strategy currently under development are contact lenses impregnated and eluting a variety of different pharmaceutical agents. For patients who wear soft contact lenses, the current options for treatment of allergic conjunctivitis are limited. Topical drugs currently available, including ketotifen and olopatadine, are not recommended for use while soft contact lenses are in place due to the preservative benzalkonium chloride (BAK). For many patients, this translates to spectacle use during high allergy seasons in order to be able to instill anti-allergy drops and achieve symptomatic relief. There have been a variety of clinical trials in the past several years directed towards creation of drug-eluting daily disposable soft contact lens (DDSCL) [16]. The first DDSCL, Acuvue® Theravision™ with Ketotifen (ATK) (Johnson & Johnson Vision Care, Inc., Jacksonville, Florida, USA), was approved by the FDA in April of 2022. Prior to approval, multiple case studies were performed demonstrating subjective and objective improvement with use of ATK during high allergy seasons, with symptomatic relief of itch, and improvement in clinical features, including episcleral, ciliary and scleral injection, as well as extent of papillary reaction [17, 18]. It is thought that the ketotifen within the DDSCL is gradually released into lacrimal fluid below CL, to maintain therapeutic levels for longer, in contrast to topical drops, which have a more temporary effect as they are washed from the tear film.

A further consideration of a DDSCL as a therapeutic strategy is that a contact lens serves as a physical barrier, much like a bandage contact lens (BCL), in addition to the potential for a slow, sustained release of medication. As such, a DDSCL may be a parsimonious solution for a patient with both dry eye and ocular allergy. One current limitation of this specific therapy is that the toric options for DDSCL are currently limited to astigmatic errors of less than 1 diopter [16]. There have been additional studies regarding the creation of DDSCL with olopatadine and DDSCL with epinastine hydrochloride, but these have not yet entered human trials [19, 20]. Nonetheless, FDA approval of ATK as the first DDSCL is promising for the ophthalmic community, as ATK may enable patients to achieve better symptomatic control during high-allergy seasons, and DDSCL technology may expand to other ophthalmic conditions and enable patients to achieve better compliance with and tolerance of mediation regimens.

4. Novel treatments for atopic and vernal keratoconjunctivitis

Thus far we have focused primarily on novel therapies with a target audience of primarily patients who suffer from SAC and PAC. For patients afflicted by VKC, there have also been promising novel therapeutics developed over the last several years. While milder cases of VKC may be managed through topical and systemic anti-histamines, topical mast cell inhibitors, and tacrolimus ointment (0.03–0.1%), topical steroid dependence in these children is common and can result in a series of untoward side effects, including ocular hypertension, steroid-induced glaucoma and cataract. For children who are dependent on topical steroids, topical cyclosporine A (CsA, 0.5–2%) has been of great utility in partial or total reduction of topical steroid therapy. Unfortunately, topical CsA is ineffective for approximately 1/3 of children, and another 1/6 of children are still dependent on topical steroids despite topical CsA [21]. Omalizumab, a monoclonal, chimeric anti-IgE antibody has been used for allergic asthma since 1999 [22] and has recently garnered interest in the treatment of VKC. The underlying pathophysiology for the atopic triad, asthma, eczema and allergy, overlaps, with both IgE mediated and cell-mediated pathways provoking symptoms of the triad.

For patients with AKC and VKC, omalizumab has been used with some success. Delivered via subcutaneous injection, the dose and frequency of omalizumab therapy varied nearly fourfold among children, which may in part be related to the severity of the presentation and the extent of inflammatory levels in these patients [23]. Not all children had symptomatic improvement of ocular symptoms with omalizumab, which should come as no surprise, given approximately 50% of patients who suffer from VKC and/or AKC do not have an IgE-dependent immune response [24, 25]. For those children who experienced a response to omalizumab, often their symptoms of asthma and eczema improved as well [23].

Another consideration is that for some children, omalizumab alone was adequate to control symptoms, whereas for others, omalizumab alone did not adequately control symptoms. As such, there is a need for additional therapeutic targets for those with VKC and/or AKC arising through different mediators. Furthermore, omalizumab is not approved for the treatment of ocular allergy alone. Patients with severe symptoms would be best treated through multispecialty collaboration, with input from such specialties as Allergy, Immunology, Rheumatology, and/or Pulmonology for the prescription, dosing and management of these medications, as well as

monitoring of the concomitant diseases. As such, omalizumab is a promising therapy for patients with severe VKC, and may help some, but not all, reduce their treatment burden.

For patients with AKC or VKC who have an incomplete or no response to omalizumab, another promising therapeutic target interleukin-5 (IL-5). IL-5 is a powerful, proinflammatory cytokine within the cell-mediated pathway of inflammation, affecting primarily eosinophils. Mepolizumab and reslizumab are humanized monoclonal antibodies that bind directly to IL-5, while benralizumab is anti-eosinophil monoclonal antibody that binds to the alpha subunit of the IL-5 receptor [26, 27]. Although none of these drugs have been studied in regards to allergic conjunctivitis, initial reports the treatment of patients with allergic and eosinophilic predominant asthma have been promising [28]. Given the common inflammatory cascades that result in the classic atopic triad, they may be considered potential future biologic therapies for patients with AKC and VKC.

5. Conclusions

Allergic eye disease, affecting around 1 in 3 Americans, is a ubiquitous condition and will likely only increase in prevalence as global warming and climate change result in higher temperatures and humidity. Existing on a wide spectrum, from milder forms like SAC and PAC, to more severe, vision-threatening forms in AKC and VKC, treatment of allergic eye disease can be complex, as it often coexists with dry eye disease. As novel medications with vastly different mechanisms of action and routes of administration are developed to address nuanced forms of dry eye and allergic disease, physicians will have more tools to address clinical signs and symptoms of dry eye and allergic eye disease in their patients.

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