

Optimizing Refractive Outcomes in the Presence of Ocular Allergy—Toward a Comprehensive Approach to Ocular Surface Health

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Abstract

Seasonal and perennial allergic conjunctivitis are common conditions which, along with dry eye and other inflammatory disorders of the ocular surface, may present an underlying management challenge in refractive surgery. Optimizing the condition and health of the ocular surface is essential in contact lens wearers, refractive surgical candidates, and post-surgical patients alike. Achieving an optimal ocular surface demands a comprehensive understanding of ocular allergy and related ocular surface conditions, as well as a proactive therapeutic approach. Although ocular allergy has often been implicated in contact lens intolerance, research has now begun to document the potential impact of allergic conjunctivitis on refractive surgical outcomes as well. Additional studies are needed to understand the relationship of allergic conjunctivitis to concomitant ocular surface disease and long-term ocular surface health. Further investigation of the potential benefit of better management of chronic episodic ocular surface inflammation, particularly in refractive surgery, will assist with the identification of optimal therapies.

Keywords

Ocular allergy, allergic conjunctivitis, dry eye, contact lens intolerance, laser-assisted in situ keratomileusis, ocular inflammation, bepotastine besilate

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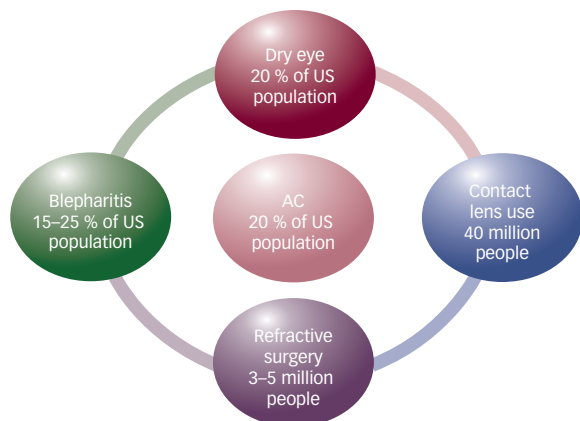
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An estimated 20 % of the US population suffers from allergic conjunctivitis,¹ related either to seasonal or perennial allergies, and the general incidence of allergy is believed to be increasing. Given its high prevalence, the signs and symptoms of ocular allergy—itching, tearing, and hyperemia—are present in a substantial subset of the patients seen in any ophthalmic practice. With the exceptions of more serious forms, such as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), and the specific management strategies for giant papillary conjunctivitis (GPC) in contact lens wearers, clinicians have typically viewed common ocular allergy as an episodic condition that is self-limiting and has little impact on the ocular surface. They respond with acute oral or topical therapy designed to provide rapid relief of signs and symptoms while getting the patient back to work or school to resume productivity. While the long-term relationship of seasonal or perennial conjunctivitis with ocular surface health, including dry eye syndrome (DES) and other ocular surface conditions, is not fully understood, there is increasing evidence that effective management of these forms of ocular allergy can play a role in improving outcomes in both contact lenses and surgical vision correction.

The allergic cascade is a component of the immune system's complex response to insult and injury and, as such, shares chemical mediators and cellular actors—not to mention signs and symptoms—with other inflammatory conditions, as well as with the mechanisms of wound healing. A complete description of the inflammatory processes that affect the ocular surface is beyond the scope of this article. However, we know that seasonal and perennial allergic conjunctivitis are immunoglobulin E (IgE)-mediated type 1 hypersensitivity reactions, involving the degranulation of conjunctival mast cells and the production of inflammatory mediators including histamines, leukotrienes, and prostaglandins. In addition to elevated IgE in serum and tear film, these conditions are also associated with eosinophil infiltration into ocular tissue, the presence in tears of cytotoxic proteins released by eosinophils, allergen-specific IgE, mast cell mediators, and evidence of upregulated adhesion molecules.²

Additionally, matrix metalloproteinase-9 (MMP-9) levels are significantly elevated in the tear film in a variety of ocular surface conditions, particularly allergy and conjunctivochalasis.³ Playing a role in both wound

Figure 1: Incidence of Allergic Conjunctivitis with Other Ocular Surface Conditions and Vision Correction



AC = allergic conjunctivitis.

healing and inflammation, the MMP-9 enzyme is also implicated in corneal epithelial changes and the pathogenesis of dysfunctional tear syndrome.⁴

The difficulty of distinguishing between ocular surface conditions that share common pathological processes is further complicated by the fact that these conditions are often concomitant, particularly dry eye and ocular allergy (see *Figure 1*). The results of a recent survey of 689 patients revealed that nearly 58 % of those who reported itching associated with allergic conjunctivitis also complained of ocular dryness. Conversely, 45 % of the patients reporting dryness also reported itching.⁵ A patient may have dry eye secondary to allergy or its treatment, or experience more severe symptoms of allergic conjunctivitis because of underlying dry eye. Furthermore, eye rubbing resulting from either condition may stimulate the inflammatory cascade and increase the severity and duration of symptoms.⁶

Impact of Allergy on Refractive Outcomes

Even on the basis of this simplified overview, it becomes evident that the interplay between inflammatory cytokines, immune cells, and enzymes on the ocular surface has the potential to create diagnostic and therapeutic challenges in any patient, but particularly those with allergic conjunctivitis and/or dry eye seeking vision correction. Ocular allergy and other inflammatory conditions must be controlled as a prerequisite to refractive surgical intervention in order to reduce complications and improve outcomes following the intervention.

Contact Lens Wear

More than 40 million Americans wear contact lenses.⁷ Results from a national survey of lens wearers suggest that more than half of them (54 %) suffer from ocular allergy.⁸ Contact lenses themselves may induce low levels of ocular surface inflammation, affect the structure, integrity, and evaporation of tear film, and trap allergens on the ocular surface. Consequently, contact lens wearers are often advised to stay out of their lenses during peak allergy season. Although the exact impact of allergic conjunctivitis on contact lens drop-out has not been documented, allergy must be a significant contributor to contact lens intolerance and discomfort. Until recently, however, much of the

attention on minimizing drop-out was focused on changing the lens material, treating dry eye, or addressing any sensitivity to components of the care system.

Several studies have demonstrated that treatment with topical antihistamine/mast cell stabilizers improves ocular comfort and lens wear time in patients with symptoms of ocular allergy.^{9,10} This research suggests that a more aggressive approach to treating ocular allergy may improve contact lens tolerance in susceptible patients—a suggestion that needs to be validated by further studies.

Although the availability of new lens materials has increased interest in the potential role of contact lenses in treating allergic conjunctivitis¹¹ or facilitating the delivery of topical anti-allergy medication, it should be noted that product labeling for ophthalmic antihistamine/mast cell stabilizers specifies that patients should remove their lenses prior to instilling the medication and wait 10 minutes before reinserting them.

Refractive Surgery

Contact lens intolerance is a leading reason why patients seek refractive surgery. As contact lens intolerance is often related to allergic conjunctivitis, it is likely that many of our surgical candidates have underlying ocular allergy. When evaluating these patients, we must confirm this diagnosis and identify appropriate management strategies for before and after surgery.

Uncontrolled allergy is an absolute contraindication for laser-assisted in situ keratomileusis (LASIK) and ocular allergy is now appreciated as a risk factor for complications following LASIK and other refractive surgical procedures. In one study, untreated allergic conjunctivitis was identified as a significant risk factor for late-onset corneal haze and myopic regression after photorefractive keratectomy (PRK), although a subsequent study by the same group found that allergic conjunctivitis did not appear to affect visual acuity following LASIK.^{12,13} However, atopy (presenting as hay fever or asthma) has been shown to be a patient-specific risk factor for the development of diffuse lamellar keratitis (DLK) following LASIK.¹⁴

The role of ocular allergy in surgical outcomes is further complicated in LASIK because of its association with post-operative dry eye. The transection of corneal nerves resulting from keratectomy decreases corneal sensitivity, leading to decreased tear production and blink rate. LASIK is also associated with immediate post-operative reductions in goblet cell density and mucin, contributing to tear film dysfunction.¹⁵

In addition to the related mechanisms of ocular inflammation and their impact on wound healing and ocular surface rehabilitation, these complications may also result from mechanical trauma or damage to the flap if patients rub their eyes in response to ocular itch. Effective management of ocular allergy therefore becomes important to prepare the patient for a refractive intervention and to ensure a stable outcome well after surgery.

In any setting where a healthy ocular surface is a prerequisite, where inflammatory processes are initiated, or where mechanical damage to

a healing surgical wound would be disadvantageous, uncontrolled or poorly controlled allergic conjunctivitis may cause untoward complications. This is particularly important in an age of premium intraocular lens implant surgery, in which patients have high expectations for rapid visual rehabilitation and excellent unaided vision immediately following the procedure. The fact that all the age-related risk factors for poor ocular surface health may be present in our cataract or glaucoma filtering surgery patients—including chronic contact lens wear, ocular allergy, DES, effects of long-term application of preservatives, conjunctivochalasis, and smoking—makes comprehensive evaluation, accurate detection, and effective treatment essential components of peri-operative management.

Despite the continued evolution of ophthalmic surgical technology, ocular surface management will remain important. For example, in laser-assisted cataract surgery, placement of the suction ring may be impeded or impossible in patients with conjunctivochalasis or chemosis.

Management Approach

The etiological and pathogenic relationships between allergy and dry eye, as well as other inflammatory conditions of the ocular surface and lid margins, have not been fully articulated and present a management challenge as we seek to optimize ocular surface health around refractive surgical interventions. Although diagnostic tools and techniques are improving, particularly for determining tear film osmolarity or detecting the presence of inflammatory mediators, clinicians are often left to tease apart these overlapping conditions empirically.

We recently published a stepwise approach to the pre-operative work-up and medical management of prospective LASIK patients, modified from the recommendations of the Joint Task Force on Practice Parameters (American College of Allergy, Asthma, and Immunology [ACAAI]/American Academy of Allergy, Asthma, and Immunology [AAAAI]) for the treatment of allergic conjunctivitis. This algorithm involves close collaboration between the ophthalmologist and the allergist/immunologist to diagnose and successfully manage ocular surface disorders and any underlying systemic conditions, with the goal of optimizing the ocular surface prior to surgery.¹⁶ The algorithm reflects the multifactorial and concomitant nature of ocular allergy, as well as suggesting that the optimal management approach may be interdisciplinary. In that regard, it provides a useful model for managing the ocular surface to reduce inflammation caused by a variety of overlapping conditions, regardless of the refractive intervention.

In patients with diagnosed allergy and/or dry eye, our goals post-LASIK are to increase ocular comfort and improve visual acuity by decreasing inflammation, stabilizing the tear film, increasing aqueous production, and promoting epithelial healing. We also want to protect the integrity of the corneal flap and avoid inducing additional inflammation by preventing eye rubbing. Prevention of ocular itch is therefore paramount.

Evidence is mounting that better control of allergy, specifically, can reduce complications. For example, Boorstein et al. found that pre-operative prophylaxis of atopic symptoms with systemic antihistamines minimized the incidence of DLK post-LASIK.¹⁴

Therapy Selection

Particularly when viewed within the full spectrum of ocular inflammatory conditions, the management of ocular allergy to optimize outcomes for vision correction has three important requirements, regardless of the refractive technology or procedure chosen. The first is that the therapeutic intervention for allergy should not induce ocular surface dryness or exacerbate DES. This is critical for both contact lens tolerance and post-surgical wound healing/ocular surface care, and may mean that the use of even second-generation oral antihistamines should be avoided, despite their potential efficacy, because of their well-documented drying effects.^{17,18} The selection of topical therapy is driven by disease severity, beginning with artificial tears and cold compresses for minor symptoms all the way up to pulsed topical corticosteroids for severe inflammation, topical cyclosporine for DES, and systemic immunotherapy. In the majority of cases, a topical combination antihistamine/mast cell stabilizer is the cornerstone of therapy.

With regard to this class of medications, the second (and related) consideration in therapeutic decision-making is the mechanism of action. Ideally, we would select a topical antihistamine/mast cell stabilizer with high specificity for the histamine-1 (H1) receptor, the principal mediator of ocular itch, and little affinity for off-target receptors associated with drying (particularly adrenergic and muscarinic receptors), good potency in mast cell stabilization, and a range of additional mechanisms that suppress other components of the early and late phases of the allergic cascade. There is some evidence that different topical antihistamine/mast cell stabilizer agents may have variable impact on tear production,¹⁹ so clinical evidence that dry eye is not exacerbated would also be helpful when choosing a therapy.

Lastly, because compliance with treatment is important, particularly in treating allergic conjunctivitis to prepare the ocular surface for surgery or improve contact lens tolerance, the comfort of the medication must be considered.

Bepotastine besilate ophthalmic solution 1.5 % (BEPREVE®, ISTA Pharmaceuticals, Inc., Irvine, CA) meets these criteria well and has advantages for contact lens or refractive surgery patients as an antihistamine/mast cell stabilizer with rapid efficacy and excellent tolerability. Bepotastine besilate is a highly selective H1 receptor antagonist and a potent inhibitor of mast cell degranulation.^{20,21} Studies in laboratory and animal models of systemic allergy and allergic conjunctivitis have suggested that it may also inhibit interleukin-5 (IL-5) production and eosinophil migration to ocular inflammatory sites, leukotriene B₄ and leukotriene D4 activity, and platelet-activating factor (PAF) activity.^{22,23}

In well-controlled clinical studies, BEPREVE was shown to be safe and well tolerated, with approximately 25 % of patients experiencing a mild, transient taste following instillation and 2–5 % of patients reporting eye irritation, headache, or nasopharyngitis.²⁰ Ocular comfort ratings for BEPREVE on instillation and five minutes post-instillation were comparable to placebo.²⁴ No dry mouth, dry eye, or drowsiness was reported by patients in the active arms. In fact, BEPREVE was associated with less dry eye than placebo.²⁵ The combination of H1 specificity with activity against other components of the early and late phases of the

allergic cascade, the absence of induced drying, and excellent ocular comfort, complement its rapid and sustained efficacy to make BEPREVE particularly useful in the refractive surgery setting.

Conclusions

The correct diagnosis and effective treatment and/or prevention of allergic conjunctivitis, particularly in the presence of other ocular surface disorders, may have greater influence on the outcomes of vision correction than previously thought. Research has begun to establish whether untreated or undertreated ocular allergy is implicated in contact lens drop-out and whether it is a risk factor for post-operative

complications, and to demonstrate that active management of allergic conjunctivitis can contribute to improvements in these outcomes. The impact of suboptimally managed ocular allergy on the success of various refractive interventions suggests that a more comprehensive approach to understanding and maintaining a healthy ocular surface may be beneficial and warrants further investigation. By continuing to improve our understanding of the complex etiological interrelationships between ocular surface conditions and the physiological responses to allergens, surgical and mechanical trauma, and wound healing, we will be able to achieve more effective management of the ocular surface in all of our patients. ■

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