

Allergic conjunctivitis: Update on pathophysiology and prospects for future treatment

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Allergic conjunctivitis is in actuality a group of diseases affecting the ocular surface and is usually associated with type 1 hypersensitivity reactions. Two acute disorders, seasonal allergic conjunctivitis and perennial allergic conjunctivitis, exist, as do 3 chronic diseases, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis. The ocular surface inflammation (usually mast cell driven) results in itching, tearing, lid and conjunctival edema–redness, and photophobia during the acute phase and can lead to a classic late-phase response (with associated eosinophilia and neutrophilia) in a subset of individuals. As is the case in other allergic diseases, a chronic disease can also develop, accompanied by remodeling of the ocular surface tissues. In severe cases the patient experiences extreme discomfort and sustains damage to the ocular surface. For such cases, there is no highly effective and safe treatment regimen. Topical administration of corticosteroids is used in severe cases but is associated with an increased risk for the development of cataracts and glaucoma. Thus there is a worldwide search for new biotargets for the treatment of these diseases. Here we provide a brief update of the clinical symptoms associated with these diseases, the rationale for disease classification, recent advances in our understanding of the pathogenesis of the diseases, and an update on both preclinical and clinical advances toward refined therapies for these diseases. (*J Allergy Clin Immunol* 2005;115:118–22.)

Key words: Allergic, eye, conjunctivitis

SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

Although there are several types of ocular allergy, seasonal and perennial allergic conjunctivitis (PAC)

Abbreviations used

AKC: Atopic keratoconjunctivitis
PAC: Perennial allergic conjunctivitis
SAC: Seasonal allergic conjunctivitis
VKC: Vernal keratoconjunctivitis

represent the majority of all ocular allergy cases, whereas the severe conditions of atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) affect a smaller group of patients. Fig 1 shows representative photographs of eyes from individuals with the various forms of allergic conjunctivitis and also provides unique features distinguishing the forms of the disease. The incidence of the severe ocular allergy varies markedly with geographic region, with individuals in Italy, Japan, and other warm climates being more likely to have these conditions. Despite these differences in disease classification and incidence, the allergic response in conjunctivitis is typically elicited by ocular exposure to allergen that causes cross-linkage of membrane-bound IgE, which triggers mast cell degranulation, releasing a cascade of allergic and inflammatory mediators. One such mediator, histamine, is the primary contributor to the development of early-phase signs and symptoms of seasonal allergic conjunctivitis (SAC),¹ usually in distinct waves that reflect allergen exposure.

The pathognomonic symptom of ocular allergy is itching. Without itching, a condition should not be considered ocular allergy. The accompanying vasodilation appears superficial and pink rather than a deep red. Chemosis, swelling of the conjunctiva, can be present, although it is usually subtle and thus only visible on slit lamp examination. More readily observable is the glassy appearance of the eye. Swelling can also become apparent in the lids. Although lid swelling peaks within 15 to 30 minutes after exposure, it tends to dissipate slowly and is often more visible on examination. Although transient, the initial intensity of this swelling can induce structural changes in the delicate collagen fibers of the skin surrounding the eye.^{2,3}

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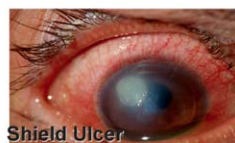
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Seasonal Allergic Conjunctivitis

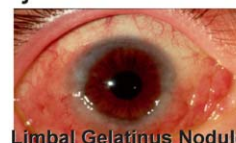


- Hallmark symptom of itching
- Accompanying chemosis (more so if patient is rubbing the eyes) and redness.
- Signs & symptoms correspond to level of allergen exposure

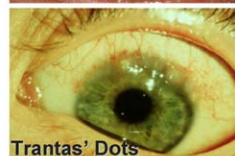
Vernal Keratoconjunctivitis



Shield Ulcer



Limbal Gelatinous Nodules



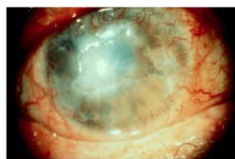
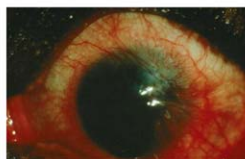
Trantas' Dots



Superior Cobblestone Papillae

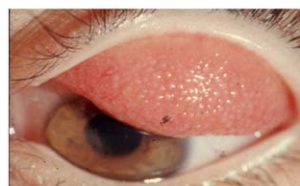
- Severe inflammatory disease, usually has seasonal recurrence
- Characterized by intense itching, tearing mucous secretion and photophobia

Atopic Keratoconjunctivitis



- Severe ocular allergic disease, typically also involving lids or other non ocular structures
- Usually perennial, but can worsen in winter months; often accompanied by atopic dermatitis

Giant Papillary Conjunctivitis



- Not a 'true' ocular allergic reaction --as SAC, AKC, and VKC are.
- Caused by repeated mechanical irritation and aggravated by concomitant allergy

FIG 1. Four types of ocular allergy.

An accurate history of the ocular allergic patient typically reveals an atopic family or personal history, as well as the environmental triggers that might elicit this reaction (ie, trees, grasses, ragweed, or pet-animal dander). Signs of rhinitis, asthma, or both might also be present, including runny nose, sneezing, and/or wheezing. In one study (n = 200) approximately 90% of patients with rhinitis indicated they had experienced at least 1 day of ocular symptoms within the past week.⁴ Patient-reported signs and symptoms are critical to the diagnosis of allergic conjunctivitis because signs and symptoms might not be present at the time of the visit.

The conjunctiva represents the upper extremity of the respiratory system, which maintains a drainage system into the nose through the nasolacrimal duct. The ocular surface can be considered a relatively large collection window, having an area of several hundred square millimeters, for the entry of allergens into the body. Allergens, allergic mediators released from the mast cell, or antiallergy eye drops drain to the nose by way of this pathway, contributing to nasal symptomatology. Ocularly instilled therapy has been shown to reduce rhinitis symptoms, such as sneezing, runny and itchy nose, and blocked nostrils.^{5,6} It is hypothesized that this effect is due to the inhibition of the allergic reaction and mast cell degranulation at the ocular surface, drainage of medication to the nose through the nasolacrimal duct, or both. Additional evidence for this

pathway of drainage from eye to nose comes from the conjunctival allergen challenge model, in which the ocular instillation of allergen can induce nasal symptoms, including itching of the nose and palate, rhinitis, sneezing, and, more rarely, wheezing.^{5,6}

Cold compresses, eyewashes with tear substitutes, and avoidance of allergens are nonspecific measures to which the allergic patient can turn in attempting to alleviate allergic symptoms; however, these are often impractical or ineffective. The use of topical therapy is pharmacokinetically and clinically the most appropriate approach for the treatment of allergic conjunctivitis because it allows for direct and local application of therapy while avoiding the ocular drying effects evident with the use of systemic antihistamines.^{7,8}

SAC and PAC are ideally treated with combination antihistamine-mast cell stabilizers, the newest generation of dual-mechanism antiallergic agents. The advantage of these therapeutic molecules is the rapidity of symptomatic relief given by immediate histamine receptor antagonism coupled with the long-term disease-modifying benefit of mast cell stabilization. Not all are equivalent, and there is an extensive body of comparative studies of such agents. In selecting a dual-action agent, one should look for a potent and long-lasting agent with the ability to relieve all the signs and symptoms of allergy, including itching, redness, lid swelling, and chemosis. Patients might benefit from

single-action mast cell stabilizers, but onset of action is not immediate, typically requiring a loading period. It is important to keep in mind the heterogeneity of mast cells when selecting a dual-action or mast cell-stabilizing agent. Mast cell subtypes vary by tissue and species in parameters, including neutral protease content and responsiveness to therapeutic agents. In selecting therapy, an agent that has been developed primarily through testing on other tissues or species might have less efficacy in the human eye than would an agent developed specifically for ocular use and researched by using human conjunctival mast cells.

Topical antihistamines are also effective, although for shorter duration, and might be considered most useful for as-needed treatment of sporadic allergic reactions for which a prolonged seasonal therapy is unnecessary. In addition, corticosteroids are a treatment option, although considering the potential side effects, including cataracts, increased intraocular pressure, and corneal melts, the use of corticosteroids is typically reserved for patients not responsive to other therapy or for use in the severe forms of allergy, such as AKC or VKC. One topical nonsteroidal anti-inflammatory drug is also approved for the relief of itching associated with SAC.

VKC AND AKC

VKC and AKC are chronic allergic diseases that originate from more complex mechanisms than SAC. Eosinophils, resident conjunctival fibroblasts, and epithelial cells, mast cells, and T_H2 lymphocytes, through allergic-inflammatory endocrine-immune stimuli, provoke multiple dysfunctions in conjunctival biochemistry and histology. Giant papillary conjunctivitis is not a true ocular allergic reaction, as is the case with SAC, AKC, and VKC. It is caused by repeated mechanical irritation (as in the case of contact lens wearers) and is aggravated by concomitant allergy.

VKC is a disease of childhood, with greater prevalence in male subjects living in warm climates. In tarsal VKC, in addition to all clinical features of allergic conjunctivitis, tarsal cobblestone-like papillae are also present. In limbal VKC gelatinous yellow-gray infiltrates are observed on the limbus, the circumference of which might appear thickened and opaque, with a peripheral and superficial neovascularization. Intense itching, tearing, mucous secretion, and severe photophobia characterize all forms of VKC. Research has also documented that histaminase deficiency exists with VKC.⁹

AKC occurs more frequently in men aged 30 to 50 years. A family history of allergies, asthma, urticaria, and/or hay fever is often present. Typically, patients have atopic dermatitis or eczema since childhood, with ocular symptoms developing later in life. The primary symptom of AKC is intense bilateral itching of the lid skin, periorbital area, and conjunctiva. Tearing, burning, photophobia, blurred vision, and a stringy, rope-like mucus discharge are also observed. Atopic blepharitis is evident, with tylosis and swollen eyelids that have a scaly in-

durated appearance, with meibomian gland dysfunction and associated dry eye. The conjunctiva can be hyperemic and edematous, and tarsal conjunctival papillae are common. Gelatinous nodules can be present around the limbus with or without Tranta dots. Treatment of VKC and AKC involves the same agents used in allergic conjunctivitis, as well as pulse therapy with steroids.

The serious nature of these conditions warrants close attention, although one should keep in mind that AKC and VKC represent just 2% of all ocular allergies. Conversely, the 98% of patients with ocular allergy having SAC and PAC are much more commonly seen, and the incidence is increasing. SAC and PAC can often go undiagnosed, or the ocular component of allergic rhinoconjunctivitis can go untreated. The signs and symptoms of allergic conjunctivitis have a meaningful effect on patients' quality of life,⁴ health, and comfort. Brief diagnostic questioning, examination, and prescription of appropriate topical ocular therapy or addition of this therapy to an existing medication regimen are the keys to appropriate management of ocular allergy and maintenance of patient health and satisfaction.

PATHOPHYSIOLOGY OF OCULAR ALLERGY: IMPLICATIONS FOR DRUG DEVELOPMENT

In addition to the clinical approaches mentioned above, there is a clear need for the development of new drugs for the treatment of both SAC and the more severe forms of the disease.¹⁰ Over the past 3 years, there has been significant progress in our understanding of the pathophysiology of allergic conjunctivitis. These data have been obtained from both direct examination of patient samples—conjunctival biopsy specimens (taken from patients with seasonal or more chronic ocular allergies) and the evaluation of refined murine models of ocular allergy.

One new area of investigation has involved an analysis of the genetics of ocular allergy. It has been known for some time that different mouse strains are more or less responsive to specific allergen challenge in the eye, and the linkage analysis of these mice is now underway to define disease susceptibility genes for ocular allergy.¹¹ Notably, Bundoc and Keane-Myers¹² have identified divergent local production of IL-10 in different mouse strains and have shown that this affects the propensity of the conjunctival mast cell to become activated by allergen. Thus modulation of IL-10 production *in situ* might represent one new therapy for ocular allergy. A linkage analysis in human subjects has shown that although some susceptibility loci are shared with other allergic diseases, there are unique genetic loci (eg, the eotaxin 1 locus) associated with SAC.^{13,14} Similar genome-wide analyses for VKC are now nearing completion. It is hoped that these data will point to unique disease-associated gene products that might be exploited for new drug design.

The study of conjunctival tissue has identified both T_H1 and T_H2 lymphocytes in the conjunctiva of patients with VKC and both T_H2 -associated cytokines and β -chemo-

kines in the tears of patients with both SAC and VKC.^{15,16} More work is required to understand the pathogenetic role for the T_H cells in VKC, but the isolation of T-cell lines from patients with VKC should pave the way for such research. It is very important to determine the clonality of T cells infiltrating the conjunctiva and the functional roles of the different T-cell subsets in disease.

One growing area of focus has been on the resident dendritic cells within the conjunctiva. This stems from the pioneering work of Allam et al¹⁷ that has shown that early dendritic cell activation by allergen is a very early step in disease pathogenesis, with dermal allergy as the prototype. The T_H cells observed *in situ* in the conjunctiva of patients with VKC might contribute to disease pathogenesis by influencing the number and type of dendritic cells resident in the conjunctiva. An analysis of the dendritic cell subsets in human and mouse conjunctiva indicate that the phenotype of these key antigen-presenting cells is unusual in the conjunctiva (M. Ohbayashi and S. J. Ono, unpublished results). Thus there is a paucity of lymphoid dendritic cells in the conjunctiva. There is also (as might be expected) a remarkable dynamic change in the number and types of dendritic cells detected in the sensitized eye, providing possible opportunities for immunomodulation. Supportive of this view has been the success by us and others in treating ocular allergy in defined murine models using IL-1 receptor antagonist and CpG oligonucleotides.^{18,19} Our finding that IL-1 receptor antagonist strongly inhibits both early- and late-phase inflammation underscores the importance of the dendritic cell and other resident antigen-presenting cells in allergic conjunctivitis. We hypothesize that the arrested activation of resident antigen-presenting cells in the conjunctiva of IL-1 receptor antagonist-treated mice inhibits the release of mast cell costimulatory factors (normally produced from allergen-activated antigen-presenting cells), thus inhibiting both mast cell activation and the late-phase response. The more limited success of CpG therapy of allergic conjunctivitis in our preclinical model might indicate that topical administration of this moiety might not be effective (as opposed to systemic delivery) but might also indicate that further refinement in ocular drug delivery of CpG oligonucleotides is required for therapeutic effect. The efficiency of systemic administration of CpG oligonucleotides is consistent with what is observed in other allergies and the pleiotropic effects of CpG oligonucleotides on many immune cells.

Mast cell degranulation (either anaphylactic or piece meal) can be identified in most biopsy specimens obtained from patients with SAC or VKC and from murine models of the diseases. Thus significant preclinical research is still directed at understanding the biology of conjunctival mast cell development and activation. The Wisconsin group is doing the best work on human conjunctival mast cell activation and on the mediators released from these cells on FcεRI cross-linking.²⁰ Other work focusing on mast cell-deficient mice and chemokine gene-deficient mice is also revealing unique pathways for conjunctival mast cell priming and activation.²¹ These data indicate that β-chemokines are not only important for the recruitment of

leukocytes in the late-phase reaction but also play roles in mast cell priming and activation. The data suggest that macrophage inflammatory protein 1α is an obligate priming signal for conjunctival mast cells and that eotaxin 1 provides an important costimulatory signal for conjunctival mast cells during disease pathogenesis.²² In view of this, it is striking that eotaxin 1 is detected in both human tears and murine conjunctival homogenates in samples obtained from human subjects and animals with syndromes resembling SAC or VKC.²³

The evidence from genetic analyses and direct analyses of human and murine tissues implicating chemokines in the pathogenesis of ocular allergy suggests that the antagonism of specific chemokines, their receptors, or both might be of value in the treatment of ocular allergy. Indeed, we have reported that antagonism of the receptor for eotaxin 1 (CCR3) is able to inhibit both early- and late-phase inflammation in the murine model of ocular allergy.²⁴ Similar studies are underway for antagonism of CCR1. In a parallel approach, we have also reported that neutralization of eotaxin 1 *in situ* by using the humanized anti-eotaxin 1 antibody (CAT-213) is able to inhibit the activation of human conjunctival mast cells in an *in vitro* passive sensitization system.²⁵ Thus chemokine antagonists hold significant progress as potential future antiocular allergy drugs.

Finally, preclinical studies are also underway to probe the roles of biomolecules essential for the late-phase response. Thus work is underway to determine whether blockade of molecules required for leukocyte recruitment into the conjunctiva (eg, very late antigen 4 and vascular cell adhesion molecule 1) can inhibit the late-phase response and whether antagonism of the GPCR-CRTH2 affects early- and late-phase inflammation in ocular allergy.

In conclusion, there has been tremendous progress in the understanding of the clinical parameters of the syndromes termed allergic conjunctivitis and the cell and molecular basis of these diseases. Current efforts are focused on developing a new treatment regimen using existing pharmaceuticals and on the identification of new biotargets for rational drug design. Several targets have been identified by using genetic, RNA profiling, and proteomic methods, and antagonists have been developed. The results of these preclinical trials are now becoming available and indicate that there will indeed be a new generation of ocular anti-inflammatory drugs. We hope that some of these will prove to be safe and effective in the treatment of this major ophthalmic condition.

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