



Trends in prevalence and treatment of ocular allergy

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Purpose of review

This review describes recent findings and trends in prevalence and treatment of allergic ocular diseases. Although the major focus is on seasonal and perennial allergic conjunctivitis, related disorders will also be considered.

Recent findings

Published reports from countries around the world suggest that the spectrum of atopic diseases, including seasonal and perennial allergic conjunctivitis, is continuing its pattern of increasing prevalence, which has been well documented over the past few decades. In addition, although treatment modalities have focused on topical formulations including antihistamines and corticosteroids, there is a significant emphasis on immunotherapy as an alternative treatment modality, particularly in the USA.

Summary

Allergic conjunctivitis is a key component in the spectrum of allergic diseases that is sometimes collectively referred to as rhinoconjunctivitis. Because of its high prevalence worldwide, it exacts an increasing toll in terms of patient discomfort, morbidity, and loss of productivity. Current estimates suggest that at least 20% of the overall population suffers from some form of allergic conjunctivitis, many without ever seeking treatments. In addition, a significant proportion of patients experience chronic forms of allergy that are less responsive to existing therapies. Recent approval of immunotherapy-based treatments may address this therapeutic gap.

Keywords

allergic conjunctivitis, rhinoconjunctivitis, sublingual immunotherapy

INTRODUCTION

Ocular allergy includes a spectrum of disorders with an overlapping symptomology and progressive severity; these disorders include seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), and vernal keratoconjunctivitis (VKC). A fifth disorder, giant papillary conjunctivitis, shares some of the symptomologies of other allergic eye diseases but is primarily the result of contact lens misuse.

SAC and PAC (collectively, allergic conjunctivitis) are the most common forms of ocular allergy. Most recent estimates suggest that 15–25% of the US population, or between 50 and 85 million Americans, suffer from allergic conjunctivitis or some form of ocular allergy [1–3]. The prevalence of allergic conjunctivitis is similar in Europe, Japan, and Australia, and is increasing worldwide [4]. Although they are not life threatening, the symptoms of ocular allergy experienced by affected individuals have a significant impact on the productivity and quality of life [5,6]. More severe forms of the ocular allergy

such as AKC or VKC are rare, but can be sight threatening [7,8]. In addition, they provide pathophysiological clues that help to address more common forms of ocular allergic disease.

Triggers for allergic responses include pollens, animal dander, mold spores, and other environmental allergens. Similarly to other allergic conditions, allergic conjunctivitis may include both an early, acute phase triggered by mast cell degranulation and a late, chronic phase involving allergic inflammation [9]. Symptomology is initially driven by histamine receptor activation, whereas the delayed phase is because of a combination of proinflammatory mediators and the infiltration of immune cells such as neutrophils, basophils, and eosinophils [10].

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KEY POINTS

- Once thought to be a disease of affluence, allergic conjunctivitis is now clearly established worldwide, with prevalence increasing particularly in developing countries with sustained growth and increasingly urban populations.
- Despite being part of the overall spectrum of seasonal and perennial allergy, it is worthwhile for both clinicians and drug development professionals to consider factors that make allergic conjunctivitis distinct from conditions such as rhinitis or allergic asthma.
- New treatments should focus on more chronic forms of allergic conjunctivitis and provide treatment for those who are more likely to have a more severe form of the disease and less likely to experience significant relief of the signs and symptoms of disease from existing therapies.

AKC is a severe form of allergic ocular disease most often seen in patients 30–50 years old with multiple systemic atopic diseases; patients with AKC typically have allergic dermatitis, eczema, and allergic asthma [7[¶]]. The disease is symptomatically comparable to severe, chronic PAC, with additional symptoms including corneal involvement. The chronic nature of the disease and its associated atopic comorbidities lead to a high rate of steroid-induced complications, including cataracts and glaucoma.

VKC is a severe form of ocular allergy that preferentially affects boys between 5 and 15 years of age, living in equatorial countries [8,11]. The disease typically presents initially in the spring allergy season, but then can recur at any time of year. Two features that are classically diagnostic for VKC are tarsal papillae and limbal gelatinous infiltrates.

UPDATE ON PREVALENCE

Similarly to all allergic diseases, SAC and PAC have seen a worldwide trend toward increased prevalence over the past few decades [4]. For example, increases in SAC and PAC in children have been well documented by the International Study of Asthma and Allergies in Childhood (ISAAC) [12,13]. These earlier studies suggested a difference between children from western countries and those from more rural, less developed countries: although their overall health may be worse, the risk of developing allergic disease was substantially lower than that seen in Europe, North America, or Japan. A recent synthesis of the ISAAC data [14[¶]] clarifies this: although the general trend is valid, high prevalence of allergic conjunctivitis and allergic rhinitis in Latin America

and West Africa is somewhat inconsistent. Still other recent studies show that although prevalence among children in many countries may have stabilized, nations undergoing substantial economic growth report spikes in the prevalence of allergic conjunctivitis or symptoms associated with rhinitis or allergic conjunctivitis. A recent report comparing the prevalence of allergic conjunctivitis, allergic rhinitis, eczema, and asthma in Croatian children found significant increases in all between 2001 and 2010 [15]. The prevalence of allergic conjunctivitis in that time period went from 6.7 to 15.3%. In Brazil, the ISAAC Phase III data in 2006 revealed the prevalence of rhinoconjunctivitis at 12%, while a report in 2012 estimated the prevalence of allergic conjunctivitis at 20.7% [16]. Similar values (6.6% increase in allergic conjunctivitis and 8.1% increase in allergic rhinitis) were noted in studies that repeated the ISAAC survey paradigm 10 years after Phase III in South Africa [17]. Of equal importance are the studies establishing the impact of allergies on the quality of life and on scholastic achievement, confirming the need for effective pediatric therapies [18].

In most prevalence studies, there is rarely a clear distinction between allergic rhinitis and allergic conjunctivitis; in fact, many studies consider allergic conjunctivitis to be primarily a condition secondary to allergic rhinitis. A recent summary of the anatomical and functional relationship between the two disorders, however, serves to highlight the distinction between the two [19]. In addition, most survey data suggest that allergic conjunctivitis is often underreported by patients [20[¶]]. Despite this, patients also list ‘ocular itchiness’ as one of the most disruptive symptoms they associate with their allergic disease. This underreporting and lack of distinction between nasal and ocular symptoms impact our ability to interpret the results from clinical studies, as discussed in the following text.

Another factor in the rise in the prevalence of allergic disease that has received considerable attention in recent literature is the role of air pollution as an exacerbating factor in allergic signs and symptoms [21[¶]]. Here, the focus may be on allergic asthma, but there are many new studies that have elucidated mechanistic aspects of what some have referred to as urban allergy. In preclinical studies, exposure of conjunctival epithelium to hydrocarbons and automotive exhaust particulates stimulated synthesis and secretion of cytokines including chemotactic peptides (which act to recruit inflammatory cells), IL-4, and IL-10 [22,23]. In addition, several studies [24[¶],25[¶]] have shown that airborne automotive particulates can stimulate the IL-17

inflammatory pathway that is associated with chronic allergic conjunctivitis and allergic rhinitis.

Although laboratory studies provide new clues to potential roles of pollutants in allergy, other studies provide valuable information on the real-world exposure levels. The researchers at the University of British Columbia, Vancouver, British Columbia, Canada, have used remote sensing technology to generate global estimates of fine airborne particulate matter ($<2.5\text{ }\mu\text{m}$) and ozone with high resolution [26]. They estimate that 89% of the world's population lives in areas where the levels of particulate matter (2.5) exceed the WHO guidelines for air quality. By comparing remote sensing data from 1990 with data from 2005, they found a '6% overall increase in particulate matter (2.5) and a 1% decrease in global population-weighted ozone concentrations was apparent, highlighted by increased concentrations in East, South, and Southeast Asia and decreased concentrations in North America and Europe'. This shift follows the pattern of increases in allergic diseases in these regions.

THERAPEUTIC UPDATE

Topical antihistamines, including antihistamine/mast cell stabilizers, remain the agents of choice for treatment of allergic conjunctivitis [10], especially with the availability of once-daily dosing [27]. Beyond these, there remains a need for more effective treatments for AKC and VKC and even for those with the more severe forms of PAC that are often less responsive to traditional therapies. Although topical and systemic steroids remain the treatment of choice for such conditions, a number of recent trials are testing alternative therapies that may avoid adverse steroid effects. For example, a recent meta-analysis confirmed that the anti-immunoglobulin E monoclonal antibody omalizumab (Novartis, Basel, CHE, Switzerland) was efficacious in patients with severe rhinitis or rhinoconjunctivitis without significant adverse effects [28]. Although such treatments may not be cost-effective, a host of biological targets, such as TNF- α , IL-4, and IL-13, may represent valuable treatment targets for future small-molecule therapies [29].

Many trials have tested calcineurin inhibitors (cyclosporine, tacrolimus) for VKC [30–32], including several that are currently underway (NCT02057822, NCT01751126). Although physicians in Europe have been using these compounds to treat VKC for decades, controlled trial data are still lacking. A recently published Japanese trial did present promising data on tacrolimus for chronic allergy with proliferative lesions or corneal involvement [32]. The study was observational and did not

include a placebo group, but did include cohorts of patients unresponsive to cyclosporine or steroid therapy. Both groups showed significant improvement in both signs and symptoms of chronic inflammation within a month of initiating therapy. Adverse effects were minimal, with 3.2% of 1436 patients reporting a burning discomfort upon application. A formulation of cyclosporine, Restasis (Allergan), is the only Food and Drug Administration-approved medication with an indication for dry eye; this, as well as the success of calcineurin inhibitors in treating VKC suggests that other dry eye treatments might also be appropriate for relief of chronic allergy. This idea was tested in a trial of rebamipide (Otsuka Pharmaceuticals, Tokyo, Japan), a topical compound approved in Japan for dry eye, for patients with either AKC or VKC [33].

These observations highlight a growing awareness that dry eye and ocular allergy, especially chronic allergy, share a common inflammatory mechanism that suggests a potential for dual-purpose or multipurpose ocular anti-inflammatory agents [34]. In addition, it is clear that the two conditions exhibit a significant comorbidity that may provide a clinical foothold in developing treatments for both conditions. The relationship between dry eye and allergic conjunctivitis was explored in another recent study that showed that conditions normally associated with enhanced dry eye symptomology that are elicited by a controlled adverse environment can also exacerbate signs and symptoms of allergic conjunctivitis [35,36] (Fig. 1). Recent discussion of new therapies for allergy has been dominated by immunotherapy, a technique of retraining or desensitizing the immune system so that responses to a specific allergen such as pollen, animal dander, or dust mites are attenuated [36,37]. This strategy for desensitization of the immune system to allergen exposure has been used for decades, but recent efforts have sought to standardize therapeutic protocols and, in the USA, have particularly focused on sublingual allergen delivery [38]. Multiple immunotherapy trials are underway or have been recently completed in the USA; the first oral agents for the treatment of grass allergy (Oralair, Stallergene Antony, France; Grastek, Merck, White House Station, New Jersey, USA) and ragweed allergy (Ragwitek, Merck) were approved by the Food and Drug Administration in 2014 (<http://www.fda.gov/newsevents/newsroom/press/announcements/ucm393820.htm>) [39]. With this in mind, it seems a good time to consider this new technique and how it might impact the therapy of allergic conjunctivitis.

Allergic diseases such as allergic rhinitis and allergic conjunctivitis involve the development of a type-2 regulatory T-cell response to common

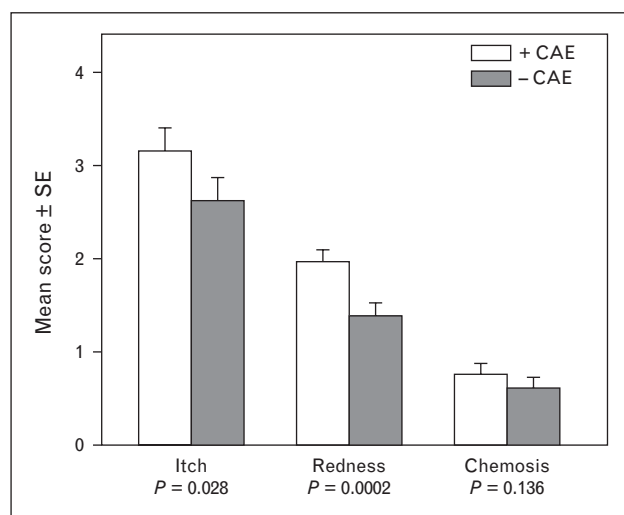


FIGURE 1. Adverse environments associated with dry eye can exacerbate signs and symptoms of allergic conjunctivitis. Patients ($n = 18$; nine in each group) with a history of ocular allergy and dry eye were randomly assigned to two groups; one group was subjected to a 30-min exposure to a controlled adverse environment (CAE), followed by a 30-min recovery, and conjunctival allergen challenge (CAC). When signs and symptoms of allergic conjunctivitis were compared between this CAE–CAC and control patients who were not subjected to CAE, all allergic conjunctivitis metrics were increased, including itch and redness, where the increase was statistically significant [36].

environmental allergens, leading to an inappropriate immunoglobulin E production and immunological sensitization [1–3,36]. When subsequently exposed to the allergenic culprit, these antibodies can initiate mast cell degranulation and the entire sequela of an allergic response. If the same antigen is exposed to dendritic cells or other antigen-presenting cells at low concentrations, it is possible to initiate a shift in the regulatory balance between the type-2 regulatory T-cells and the nonallergenic type-1 T-cells. Although this desensitization process is not completely understood, suppression of allergen-specific immunoglobulin E production is also thought to be important in immunotherapy [36].

Recent trials have focused on the delivery of allergen by a sublingual immunotherapy (SLIT) formulation rather than the subcutaneous injection route that has been the method of choice in the USA [39–42]. The protracted nature of the injection regimes had limited this therapy to the most severely allergic patients, but the most recent studies suggest a similar efficacy for oral subcutaneous delivery of antigen. Recent large-scale trials in the USA have focused on SLIT therapy for grass and ragweed allergies, and trials are underway using allergens from dust mites. Studies with other

perennial and seasonal allergens are likely to follow, and although there are no available studies comparing sublingual allergen delivery with subcutaneous methods, there does seem to be fewer overall adverse effects [43]. A sample of recent trials in the USA is summarized in Table 1. Note that few of these studies use any primary measures of allergic conjunctivitis as endpoints.

Concerns about immunotherapy safety and the risk of anaphylaxis were addressed in recent meta-analyses of SLIT that included thousands of patients over a wide range of allergen doses and delivery protocols [44,45^{*}]. These studies concluded that there was very little risk of anaphylaxis associated with the treatment. In addition, evidence suggests that relief from signs and symptoms of allergy can develop with weeks of therapy initiation, and that this relief is sustained even after a discontinuation of allergen. On the contrary, despite the large number of trials, there still seems considerable debate over dosing issues. In addition, the high numbers of recent trials for grass, ragweed, and dust mite allergens have been unable to specifically address the efficacy of SLIT for allergic conjunctivitis [45^{*}].

Patients with allergies commonly experience a spectrum of symptoms that includes ocular itching, hyperemia, and chemosis. More than 80% of allergy sufferers report experiencing some ocular symptomatology. Despite this, immunotherapy trials have only limited measures of ocular symptoms often included in score based upon ‘gritty eyes or watery eyes’. None of the scores appears to include direct measures of ocular itching, the hallmark symptom of allergic conjunctivitis [44,46]. Despite this limitation, all of the newly approved SLIT therapies include an indication for use as ‘an allergen extract indicated as immunotherapy for treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis’ (<http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenic/UCM393184.pdf>).

To date, there are no head-to-head studies comparing any immunotherapy agents to a positive comparator group such as antihistamine or steroid therapy. Most clinical trials do include rescue drug usage (either systemic, nasal, or ocular) as a secondary endpoint, but this does not provide a direct comparison between immunotherapy and established allergy treatments. This study [47] design may be a reflection of the low statistical power inherent in all environmental trials.

Unlike treatments for allergic rhinitis, therapies targeted to allergic conjunctivitis typically achieve regulatory approval using controlled allergen challenge protocols such as the CAC, with or without additional environmental trials. Allergen challenge has been used to measure efficacy of allergen

Table 1. Recent clinical trials of immunotherapies for allergic conjunctivitis or allergic rhinitis^a

Allergen	Clintrials/sponsor	Primary endpoint	Conjunctivitis endpoint	Study results
Grass (Phase III)	NCT00409409/Stallergenes	TSS ¹	Itching, watery eyes component of TSS ¹	Complete, not reported
Grass (Phase III)	NCT00550550/Merck	TCS ²	Gritty/itchy/red eyes component of DSS ³	Met primary endpoint vs. placebo
Grass (Phase IIb/III)	NCT00367640/Stallergenes	TSS ¹	Itching, watery eyes component of TSS ¹	Complete, not reported
Ragweed (Phase III)	NCT01353079/Greer Labs	TCS ²	None specified	Complete, not reported
Ragweed (Phase II)	NCT01198613/Circassia Ltd	TCS ²	Ocular symptom score	Met primary endpoint vs. placebo
Ragweed (Phase III)	NCT00770315/Merck	TCS ²	Gritty/itchy/red eyes component of DSS ³	Met primary endpoint vs. placebo
Dust mites (Phase II/III)	NCT00674700/Stallergenes	TSS ¹	Itching, watery eyes component of TSS ¹	Complete, not reported
Dust mites (Phase III)	NCT01700192/Merck	TCS ²	None specified	Study not complete

1 TSS, total symptom score; 2 TCS, total combined score; 3 DSS, daily symptom score.

^aIncludes examples from 161 studies found in Clintrials.gov database by searching *immunotherapy* and *grass* (91 studies), *ragweed* (23 studies), or *dust mites* (47 studies).

desensitization, and can provide an objective measure of the treatment effects on either nasal or ocular symptoms. In several trials, a conjunctival challenge component has been included as a secondary endpoint [48,49]. Such measures are attractive as alternative or complementary assessments of treatment efficacy; for example, one study [49] examining the specificity of immunotherapy showed a 16–31-fold increase in the threshold for conjunctival response to allergen provocation. This study also highlighted a critical distinction between SLIT and more traditional therapeutics: immunotherapy provides protection against a single allergen, whereas antihistamines, mast cell stabilizers, and corticosteroids act to modify allergic responses to all allergens. Future refinement of endpoints and outcome assessments will be critical in the use of SLIT as a therapy for allergic conjunctivitis going forward [46].

CONCLUSION

Allergic conjunctivitis and related ocular allergies represent an important aspect of allergic disease with a significant unmet need for effective therapeutics and a growing worldwide prevalence. Future efforts should target the more chronic forms of the disorder while working to refine the encouraging new approaches represented by immunotherapy.

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Conflicts of interest

P.J.G. is the Vice President with the Department of Allergy, Ora, Inc, Andover, MA, an organization that consults and conducts sponsored and independent research and clinical trials in the field of ocular allergy. Ora, Inc has received compensation for conducting clinical trials from sponsors including Allergan, Inc (Irvine, USA), and Alcon, Inc (Fort Worth, USA).

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