

# Ocular Allergy: an Updated Review

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## Abstract

Ocular allergy encompasses an inflammatory reaction of the surface of the eye that is caused by inappropriate response of the ocular surface to various environmental allergens. Since the majority of this inflammation involves the conjunctiva, the term “allergic conjunctivitis” is often used interchangeably with ocular allergies. Ocular allergy is a common problem that affects people of all ages in which the presentation may vary from being asymptomatic in mild cases to serious and vision threatening inflammation in severe cases. Subsets of ocular allergy include the predominantly ocular itch-inducing seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC) to more severe sight-threatening vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC).

The management of allergic conjunctivitis ranges from simple life style modifications and the regular use of pharmacologic therapy both topical and systemic, to more advanced therapy including allergen specific immunotherapy and a newly introduced anti-IgE antibody novel therapy.

**Keywords:** Ocular allergy; Allergic conjunctivitis; Seasonal; Perennial; Vernal; Atopic

## Introduction

Ocular allergy affects up to 40% of the population in the United States where allergic conjunctivitis considered the most common cause of conjunctivitis. Patients living with symptoms of ocular allergy endure a lower quality of life secondary to ailments that can range from ocular discomfort to vision loss [1,2]. Patients may also suffer from the financial burden inflicted by the need for adequate management, which can be life-long [2]. Furthermore, the global prevalence of ocular allergies has steadily been on the rise, elevating the burden of this disease on the society [3].

Ocular allergy is often associated with nasal allergy symptoms, hence the term ‘rhinoconjunctivitis’. Sixty four percent of patients with symptoms of allergic rhinitis report associated conjunctival symptoms of ocular allergy [4].

A study of patients with hay fever found that ocular symptoms alone were experienced in 8% of the study population, while 85.3 % of the study population has a combination of both eye and nasal symptoms [5].

Since the majority of the ocular allergic inflammation involves the conjunctiva, the term “allergic conjunctivitis” is often used interchangeably with ocular allergies [1,2]. Disorders that fall under the category of allergic conjunctivitis range from predominantly ocular itch-inducing seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC) to more severe potentially sight-threatening Vernal keratoconjunctivitis (VKC), Atopic keratoconjunctivitis (AKC), as well as some other disorder that

will be discussed later. The management of ocular allergy ranges from the simplest measures to the most complex pharmacotherapy, immunotherapy and monoclonal antibodies [6].

This manuscript highlights the classification of ocular allergy and provides details on the management options of ocular allergy that include style modifications and the use of topical and systemic medications. In addition the manuscript provides some insight on the use of immunotherapy in the treatment of the most severe forms of ocular allergy and the recent advance in the use of monoclonal antibodies.

## Classification

As mentioned earlier, the conjunctiva is the most common ocular structure to be involved in ocular allergy, hence allergic conjunctivitis is used interchangeably. The traditional classification methods of allergic conjunctivitis stems from the cause of the ocular allergy, and can be described as seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis, and giant papillary conjunctivitis.

### Seasonal Allergic Conjunctivitis (SAC) and Perennial Allergic Conjunctivitis (PAC)

SAC and PAC comprise most of the allergic conjunctivitis cases (about 95% in the United States) [7]. Although SAC and PAC are the most common, the proportion of the more severe forms of ocular allergic disease (AKC, VKC) increase in countries in the southern hemisphere [8]. Theories to explain this include increasing levels of industrialization and pollution or simply an anomaly arising from under-reporting of milder conditions [8].

SAC and PAC are distinguished from each other mainly by the timing of exacerbations that could be related to different stimulating allergens in each [9]. SAC (commonly called hay fever conjunctivitis) is more common than PAC and worse during spring and summer times. The most frequent allergens responsible are mold spores or tree, weed, or grass pollens, however the specific allergen varies with geographic location [4]. PAC causes symptoms throughout the year, generally worse in the autumn when exposure to house dust mites, animal dander, feathers and fungal allergens is greatest. It is less common and tends to be milder than the seasonal form [10,11]. The hallmark symptoms of both SAC and PAC are itching and redness that are usually bilateral. Other symptoms include burning sensation and watering or sometimes mild mucoid discharge [10]. The conjunctivae are usually mildly injected with various levels of chemosis [11]. Although the symptoms are usually bilateral, the degree of involvement may not be symmetric. Cobblestoning is a sign generally not observed in the SAC or PAC and indicates a more chronic and severe form of allergic conjunctivitis although fine papillary hypertrophy of the upper tarsal conjunctiva may occur [12,13]. The cornea is not usually involved in SAC or PAC [11,12].

### Vernal Keratoconjunctivitis (VKC)

VKC is a more serious and potentially sight threatening form of ocular allergy in which the stimulant (allergen) is usually not known [14]. It is a chronic bilateral disease that typically affects young males and usually resolves after puberty [14,15]. There is a history of eczema or asthma in 75 % of the patient [16]. VKC has a wide geographical distribution, and usually occurs in warm, dry areas [17].

KC can be classified to Palpebral, limbal and mixed forms. Palpebral form primarily involves the upper tarsal conjunctiva and may be associated with significant corneal involvement as a result of the close

apposition between the inflamed conjunctiva and the corneal epithelium [16,18]. Limbal form typically affects black and Asian patients and is usually limited to the perilimbal area. Mixed VKC basically has features of both palpebral and limbal disease [16,18]. Patients usually have a year-round disease but seasonal flare-ups are common. The main symptom of VKC is itching. Other common symptoms include tearing, mucus discharge, photophobia, pain, burning and foreign body sensation [16,18]. The signs are mostly confined to the conjunctiva and cornea, while the eyelid skin is relatively uninvolved [18]. The hallmark finding of VKC is the cobblestone-like giant papillae of the upper tarsal conjunctiva [16,18,19].

Bulbar conjunctiva is usually edematous and injected. The perilimbal conjunctiva may be thickened and edematous forming a gelatinous-like hypertrophy [18]. Limbal nodules and Trantas dots composed of eosinophils and dead epithelial cells may be observed [16]. These limbal changes may sometimes lead to superficial neovascularization of the cornea and pannus. The most important and vision threatening complications occur in the cornea as mild epithelial keratitis or in more severe cases as shield ulcers. [16,18]. A shield ulcer results from chemical damage to the epithelial surface by mediators released from mast cells and eosinophils. Shield ulcers are typically oval or pentagonal, superficial, and superiorly located with grayish opacification of the bed and elevated margins [18]. They may take months to re-epithelize and in chronic advanced cases they may form an opaque white or yellow plaque [18]. It is also known that there is a strong association between VKC and keratoconus [18].

### **Atopic Keratoconjunctivitis (AKC)**

AKC was first described by Michael Hogan in 1952 as an allergic keratoconjunctivitis occurring in association with allergic dermatitis [20]. AKC occurs in both children and adults and is associated with eczema of the lids or of other parts of the body [20]. AKC most frequently occurs in men and typically starts in the late teens or early twenties but rarely before puberty, and may persist until the fourth or fifth decade of life. The main ocular symptoms include extreme itching, photophobia, burning and foreign body sensation [20,21]. The patients usually wake up with copious mucous discharge gluing the eyes together. Eyelid disorders are the most common ocular complications of atopic dermatitis and they are often red, macerated with crusting and scaling, which are not symptoms seen in patients with VKC [21]. In severe cases of AKC conjunctival scarring with sub epithelial fibrosis, fornix foreshortening and symblepharon may occur [21]. Corneal ulceration and neovascularization may also occur. The conjunctival scarring of AKC may be confused with other cicatrizing diseases like ocular cicatrizing pemphigoid [21].

### **Giant Papillary Conjunctivitis (GPC)**

GPC is usually seen in patients with contact lenses, but also can be seen in patients with corneal foreign bodies, exposed sutures, ocular prosthesis and extruded scleral buckle [22]. GPC is described as papillae on the upper tarsal conjunctiva with a size of 1 mm or larger in diameter [22]. Also papules with a size of 0.3 mm or larger associated with the symptoms of itching, contact lens intolerance or conjunctival injection, meet the criteria for the diagnosis of GPC [23].

Patients with GPC has symptoms of contact lens intolerance, blurry vision, excessive mucous secretion, itching and ocular irritation [22,23]. It is important to mention that large papillae in the medial and lateral aspects of the upper tarsus and the ones along the tarsal border should not be used in evaluation as they may be seen in normal individuals. It is to be mentioned that the hypertrophied papillae in the tarsal conjunctiva can sometimes lead to ptosis [22,23].

### **Other Ocular Allergy Disorders**

Other ocular surface allergy disorders that may be confused with

the above mentioned ocular syndromes and considered part of the differential diagnosis include both contact blepharo-conjunctivitis and phlyctenular keratoconjunctivitis

### **Contact Blepharo-Conjunctivitis**

This refers to the acute or subacute reaction that is seen most commonly as a reaction to eye drop constituents or sometimes as a reaction to contact lens solutions [24]. It usually happens in the early course of treatment but can be seen after chronic use of the same drop. The signs predominantly involve the eyelid skin (erythema, thickening, induration), although there may be a conjunctival reaction [24]. It appears that the preservative may be largely responsible for allergic, toxic or inflammatory reactions, although antiglaucoma and antibiotic drops are not uncommon causes [24].

### **Phlyctenular Keratoconjunctivitis (PKC)**

PKC is a nodular inflammation of the conjunctiva or cornea that results from a hypersensitivity reaction to a foreign antigen. Conjunctival involvement is usually transient and asymptomatic, but corneal involvement can occur in various forms and can lead to visual impairment. In the past, tuberculin protein was thought to be the main antigen responsible for PKC, however, with improvement of public health, microbial proteins of staphylococcus aureus were found to be the most common causative antigens in PKC. Risk factors for staphylococcus aureus exposure include chronic blepharitis and suppurative keratitis. PKC is more common in females and has a higher incidence during spring [25]. The clinical presentation of PKC varies depending on its location as well as the underlying etiology. Conjunctival lesions may cause only mild to moderate irritation of the eye, while corneal lesions typically may have more severe pain and photophobia. More severe light sensitivity may occur with tuberculosis related phlyctenules compared to S. aureus related phlyctenules [26]. PKC presents as a nodular lesion with injection of the surrounding conjunctival vessels and may show some ulceration and staining with fluorescein as they progress. Conjunctival phlyctenules occurs more commonly in the interpalpebral conjunctiva and are frequently noted along the limbal region. Sometimes, multiple nodules may be found along the limbal surface. Corneal phlyctenules usually starts at the limbal region and frequently progress to corneal ulceration and neovascularization that can lead to scarring and various degrees of vision loss. The diagnosis of PKC is made based on the history and clinical examination findings. When thinking about an infectious etiology, further investigations to rule out tuberculosis or chlamydia should be done and if positive, appropriate systemic treatment is required.

### **Pathophysiology**

SAC and PAC are classic Gell and Coombs type 1 hypersensitivity reactions, occurring as a consequence of inappropriate (atopic or "out of place) immune responses to ordinarily harmless materials which elicit an immune response in those individuals who are genetically destined to make such responses as a consequence of inadequate regulation, with IgE antibody production directed against the allergens and subsequent binding of those IgE molecules to Fc receptors on the surface of mucosal mast cells. Subsequent contact with the sensitizing allergen results in binding of allergen to those IgE molecules, and when such binding to two adjacent IgE molecules occurs, a change in membrane adenylyl cyclase occurs, changing the intracellular concentration of cyclic AMP, resulting in opening of calcium gates, with a spike in intracellular calcium concentrations. This, then results in the aggregation of tubulin subunits, forming microtubules, resulting in degranulation and a release of preformed histamine and proteases, triggering a type I hypersensitivity response [27,28]. This causes itching, tearing, edema and redness which lasts 20-30 minutes. Mast cells continue to produce late-phase reactants such as prostaglandins, leukotrienes, platelet-activating-factor and chemotactic cytokines that result in recruitment of

other inflammatory cells, producing a sustained inflammatory reaction characterized by neutrophil and eosinophil activation and increased vascular permeability and microvascular dilation [29], the so-called late phase reaction, which is subclinical in SAC and in PAC, but manifest in the more complex and vision threatening ocular allergies.

While the pathogenesis of VKC and AKC also involves -mediated chronic mast cell degranulation, the inflammation is primarily Th2 lymphocyte-mediated [30], involving a much more complex cast of cellular characters than that of SAC and PAC. In VKC, Th2 lymphocyte-derived cytokines result in an over-expression of mast cells, eosinophils, neutrophils and conjunctival fibroblasts, and the added storm of growth factors, IL-4 and IL-13 results in the growth of the extracellular matrix, culminating in the formation of giant papillae [31]. And the cytokine recruitment of eosinophils to the affected area is especially devastating, with the liberation of eosinophil major basic protein and eosinophil cationic protein, both of which are highly toxic to corneal epithelium. Thus, VKC and AKC and even GPC are complex combined Type 1 and Type 4 Gell and Coombs hypersensitivity reactions. The pathogenesis of AKC is similar, but is also thought to include Th1 lymphocyte-derived cytokines [32]. In contrast to the above, contact allergy is classified as a type IV hypersensitivity reaction [33]. During sensitization, allergens, which are simple chemicals that combine with skin proteins to form antigens, are processed by MHC class II on T lymphocytes to induce production of memory T cells [34]. Subsequent exposure results to memory T cells and the production of cytokines and proliferation of T cells. Cytokines released from Th1 cells and Th2 cells mediate the recruitment of macrophages and eosinophils, respectively, which result in the pathogenesis of conjunctivitis.

### Management of Ocular Allergy

The management of ocular allergy in general involves preventive measures, non-pharmacologic as well as pharmacologic measures.

Preventive measures include identification of provocative allergens and avoidance or reduction, as much as possible, of contact with known allergens and appropriate management of environmental exposure [35]. This is a measure at which allergists are most adept. In addition, prevention of symptoms of seasonal allergic conjunctivitis includes limiting outdoor exposure, and keeping car and home windows closed during the peak pollen seasons [35,36]. For patients with perennial allergic conjunctivitis, prevention includes avoidance of the specific allergens that are causing symptoms in a specific patient. For those allergic to dust mites, helpful measures include replacing old pillows, blankets, and mattresses. Measures also include using dust mite allergen impermeable covers for pillows, comforters, and mattresses. Additionally, other reservoirs of dust should be removed, such as old carpets, old furniture, and old curtains or drapes. If the patient is allergic to animal dander, the animal may need to be removed from the home, and old carpets, furniture, and curtains should be removed or cleaned thoroughly [35,36]. Air cleaners with frequent replacement of the filters are very useful.

The non-pharmacologic measures include avoiding eye rubbing as this result in mechanical mast cell degranulation and worsening of symptoms. This may have become a habit and thus may be very difficult to change. In addition the use of cool compresses and refrigerated artificial tears throughout the day has been found to be effective in reducing eyelid and periorbital edema and removing allergens from the eye as showed by Bilkhu et al. [36]. The use of contact lens should be limited during the acute stage of the allergic conjunctivitis.

### Pharmacologic Therapy

This includes both topical and systemic medications for acute and chronic management

Topical medications include antihistamine/vasoconstrictor combination products, antihistamines with mast cell stabilizing properties, mast cell stabilizers, and, topical glucocorticoids

### Topical Vasoconstrictors (decongestants) and Antihistamines

Topical decongestants were the first agents to be approved for the treatment of allergic conjunctivitis. Tetrahydrozoline was marketed in the 1950s and naphazoline in 1971. While decongestants are effective for ocular hyperemia, they have no effect on itching and are subject to tachyphylaxis [35]. Ocular decongestants were paired early on with topical antihistamines such as pheniramine and antazoline to combat both the itching and redness associated with allergic conjunctivitis [25,37]. These topical medications are appropriate for short-term or episodic use only. Regular use for longer than two weeks can lead to rebound hyperemia because of the vasoconstrictor component [37].

The antihistamine component competitively and reversibly blocks histamine receptors in the conjunctiva and eyelids, thus inhibiting the actions of the primary mast cell-derived mediator. The vasoconstrictor component activates the post-junctional, alpha-adrenergic receptors found in blood vessels, causing vasoconstriction and decreased conjunctival edema. Examples of topical antihistamine/vasoconstrictor drugs include naphazoline and pheniramine (available as Naphcon-A, Opcon-A, Visine-A, and others). Dosing is up to four times daily during acute symptoms. Single agent topical products (vasoconstrictors or antihistamines only) are also available without a prescription, although the combination products usually work better [37,38].

In the 1990s the most efficacious and commercially successful second generation antihistamine became available in the market and included the topical ophthalmic eye drops levocabastine and emedastine [37]. Levocabastine and emedastine were indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis and allergic conjunctivitis respectively. Levocabastine is the first topical antihistamine with multiple mechanisms that impacted both the early and late-phases of ocular allergic reactions through the upregulation of eosinophil activation and infiltration [39].

### Mast-cell Stabilizers

Cromolyn sodium (also known as sodium cromoglycate) was approved in 1984 for the treatment of vernal keratoconjunctivitis. Lodoxamide has an identical indication and was approved in 1993. Lodoxamide has a greater potency and rapidity of action than cromolyn sodium; in addition it also appears to be more efficacious against the

**Table 1:** Details of different types of ocular allergy.

Signs and symptoms	SAC/PAC	VKC	ACK	GPC
<b>White Discharge</b>	clear/mucoid	mucoid	mucoid	clear
<b>Itchy</b>	+	++	++	++
<b>Chemosis</b>	+	+/-	+/-	+/-
<b>Corneal involvement</b>	-	++	+	-
<b>Cobblestoning</b>	-	++	++	++
<b>Lid involvement</b>	-	+/-	++	+/-
<b>Seasonal variation</b>	+	+	+/-	+/-
<b>Systemic association</b>	rhinitis	-	eczema/ asthma	-

+ present; - absent; +/- present or absent; ++ pronounced. SAC, Seasonal allergic conjunctivitis; PAC, Perennial allergic conjunctivitis; ACK, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis; GPC, Giant papillary conjunctivitis.



epithelial damage and shield ulcers related to vernal keratoconjunctivitis [40]. Nedocromil sodium, was approved in 1999 for ocular itching associated with allergic conjunctivitis and has shown a greater efficacy than cromolyn sodium [41]. The full efficacy of mast cell stabilizers is normally reached 5 to 14 days after therapy has been initiated and therefore these eye drops are not effective for acute symptoms [42]. Mast cell stabilizers are administered four times daily and patients with seasonal allergic conjunctivitis should begin treatment two to four weeks before the pollen season [40-42].

### **Antihistamines with Mast Cell-stabilizing Properties**

This group of eye drops includes olopatadine, alcaftadine, bepotastine, azelastine HCl, epinastine, ketotifen fumarate, and emedastine. In the United States, Ketotifen fumarate is available in a generic form and can be purchased over the counter with no prescription. The usual dose is twice per day for most products. There are three antihistamine/mast cell stabilizing drops approved for once daily dosing – alcaftadine 0.25%, olopatadine 0.2%, and olopatadine 0.7%; only alcaftadine is pregnancy category B [43]. Onset of action is within minutes for most drugs. At least two weeks of therapy should be allowed in order to assess the full efficacy of prophylactic therapy with these agents, since it may take some time for the inflammation to be controlled and symptoms to subside completely. Side effects of these eye drops may include stinging and burning sensation. Refrigerating the drops and/or use refrigerated artificial tears prior to using these medications are effective ways to decrease burning sensation [42]. A randomized study that compared cromolyn sodium use (4 percent, four times daily) for two weeks prior to allergen challenge with a single drop of ketotifen fumarate (0.025 percent) given just before allergen challenge found that the single drop of ketotifen was superior in controlling itching and redness at 15 minutes and at 4 hours after challenge [44].

### **Nonsteroidal Anti-inflammatory Drugs**

Specific prostaglandins are thought to lower the conjunctival threshold for histamine-induced itching, and the prostaglandins may be pruritogenic themselves as well. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin and leukotriene production, thus helpful in allergic conjunctivitis [45].

NSAIDs commonly prescribed for ocular allergy include ketorolac, diclofenac, indomethacin, and flurbiprofen. However, only ketorolac is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis [46]. Although Ketorolac is the only NSAID approved for the treatment of seasonal allergic conjunctivitis, topical formulations of indomethacin, ketorolac, and diclofenac have demonstrated efficacy in the treatment of vernal keratoconjunctivitis [46].

### **Glucocorticoids**

Topical corticosteroid administration should be limited for use in patients with refractory symptoms such as symptoms associated with vernal keratoconjunctivitis and atopic keratoconjunctivitis. Topical corticosteroids are not effective in the early phase allergic reaction; however by inhibiting the production and/or release of the inflammatory mediators they are very effective in suppressing the late-phase reaction [47,48]. The long-term use of topical corticosteroids is associated with potentially serious and sight-threatening side effects themselves such as increased intraocular pressure (IOP) and risk of cataract formation [47]. Loteprednol, has been approved in 1998 for the treatment of allergic conjunctivitis. It belongs to the new class of corticosteroids that reduce the risk of increased IOP by being rapidly converted into inactive metabolites following corneal penetration [49]. Although the corticosteroid Difluprednate is mainly indicated for the management of postoperative inflammation and pain, it has been

shown to reduce both provocation-induced early phase itching, and the late-phase ocular itching and hyperemia associated with seasonal allergic conjunctivitis [29].

### **Topical Immune-Modulators**

Both cyclosporine A, and tacrolimus have been evaluated previously for the management of vision-threatening and severe vernal keratoconjunctivitis and atopic keratoconjunctivitis [50,51]. In a large prospective observational study, 594 patients with vernal keratoconjunctivitis and atopic keratoconjunctivitis were included to evaluate the efficacy of topical cyclosporine. The study showed that the use of topical cyclosporine A 0.1% significantly decreased all objective and subjective scores, including itching. In addition 44.4% of patients with VKC and 21.9% of patients with AKC stopped therapy due to complete resolution of symptoms, and approximately 30% of steroid users were able to discontinue concomitant topical steroid use. Eye irritation was the most common adverse event (4.4%) and all infectious incidents (n = 10) occurred in subjects undergoing concomitant steroid use [52].

Topical tacrolimus, used either as 0.03% ointment or 0.1% ophthalmic suspension, also appears safe and effective, and the 0.1% ophthalmic suspension may be more effective at resolving giant papillae because of VKC and AKC. Compared to cyclosporine, Tacrolimus is 100-fold more potent. It blocks cellular steroid receptors, inhibiting mediator release from mast cells and, thereby, suppressing T-cell activation and consequent B-cell proliferation [51]. Topical tacrolimus 0.3%, compared to the 0.1% and 0.005% formulation, apparently offers the optimal efficacy in treatment of ocular itching and improvement across all other subjective and objective measures [53].

### **Systemic Therapy**

#### **Oral antihistamines**

In cases of seasonal allergies, systemic over-the-counter, or prescription antihistamines may be helpful for symptoms of rhinitis and generalized pruritus. In cases of ocular symptoms, randomized trials have shown that topical antihistamines are more effective than oral medications for ocular symptoms. Specifically, topical olopatadine was more effective than oral olopatadine or fexofenadine, and topical ketotifen was more effective than oral desloratadine [54,55]. In addition, oral antihistamines can cause drying of mucosal membranes and decreased tear production in some patients, especially those with concomitant dry eye [56].

Some oral antihistamines have shown efficacy in the treatment of allergic conjunctivitis, compared with placebo, in different clinical studies [57,58]. Oral administration of antihistamines results in peak serum levels in 30 minutes to 3 hours, depending on the specific drug. Full effects are seen after several days of use. Thus, these agents have a slower onset of action compared with topical agents, unless they are taken prophylactically.

#### **Systemic immunomodulators**

Patients with refractory severe disease or vision-threatening allergy may benefit from systemic immunosuppressive therapy. Guidelines regarding systemic immunosuppressive therapy are not available in the literature except for isolated case reports [59,60].

This group of medications include the calcineurin and mTOR inhibitors Cyclosporine A, Tacrolimus and pimecrolimus. These medications have not been approved in Europe or the United States for the treatment of ocular allergy (approved only in Japan), and their use should be reserved to selected patients who are followed in referral centers. Cyclosporine A is effective in controlling ocular inflammation by blocking Th2 lymphocyte proliferation and interleukin 2 (IL) productions. It also inhibits histamine release from mast cells and

basophils and, through a reduction of IL-5 production; it may reduce the recruitment and the effects of eosinophils on the conjunctiva [59].

In a previous study it has been demonstrated that in severe cases of ocular allergy, resistant to conventional therapy, systemic treatment with T-lymphocyte signal transduction inhibitors may ameliorate both the dermatologic and ocular manifestations [60]. In this study, systemic cyclosporine A, dosed 2.5 mg/kg/day in divided doses, has been successfully used for the treatment of severe AKC and dry-eye disease. However, potential toxicity restrict long term use of these products [60].

In another study, 4 patients (aged 31-64) with severe atopic keratoconjunctivitis and atopic dermatitis refractory to or dependent on steroid therapy were treated with Cyclosporine 3 to 5 mg/kg and mean duration treatment 37 months. Ocular inflammation was controlled totally in three patients and partially in one patient [61]. In a 6 year old child with severe and vision threatening vernal keratoconjunctivitis, a dramatic improvement and stabilization of his symptoms was achieved with oral cyclosporine therapy [62].

### Allergen-specific immunotherapy

Immunotherapy as a treatment for allergic diseases, was first introduced by Noon and Freeman in 1911 as a means of treating hay fever (rhinoconjunctivitis) [63]. In this therapy, patient with allergies receives increasing doses of an allergen-containing extract, comprised of the relevant allergens to which the patient is sensitive, in an attempt to suppress or eliminate allergic symptomatology [63]. Allergen-specific immunotherapy is typically recommended for patients whose allergic rhinoconjunctivitis and asthma symptoms cannot be controlled by medication and environmental control, who cannot tolerate their medications, or who do not comply with chronic medication regimens. With continuous administration of allergens it is expected that the treatment regimen will make the patient tolerant to the offending allergen and suppress future untoward responses to the allergen(s) through modulation of the patient's immune system [64,65].

Allergen specific immunotherapy is believed to be the only therapeutic option capable of changing the natural course of allergic disease and has demonstrated long-term, disease-modifying effects [66].

Allergen specific immunotherapy may be administered by either the subcutaneous or sublingual route. It has been shown that both methods are effective at treating allergic conjunctivitis [67]. However, in patients with polysensitization, the injection method shows superior results [68].

Studies showed that symptoms of rhinoconjunctivitis had improved following the use of sublingual immunotherapy with symptom/medication score improvements of up to 27–28% for ragweed and grass pollen [69,70]. It has been recently suggested that dust mite sublingual immunotherapy may also be effective for allergic rhinitis with or without conjunctivitis. In a randomized, double-blind placebo-controlled study, authors demonstrated reduced nasal and ocular symptoms in adults treated with a dust mite sublingual immunotherapy tablet undergoing allergen challenge in an exposure chamber [71].

### Special Situations

#### Ocular allergy in pregnancy

The first step should include non-pharmacologic measures and allergen avoidance. If such measures do not control symptoms adequately, cromolyn sodium eye drops may be tried next. If allergen exposure is predictable (eg, pollen season), therapy should be initiated two weeks before [72].

If cromolyn sodium eye drops are not enough to control the symptoms, antihistamine eye drops may be used. Although these agents were assigned a category C by the US Food and Drug Administration

(FDA) in the past, reports of adverse effects are lacking and most ophthalmologists are comfortable with their safety [72].

Topical glucocorticoids should be used with caution in pregnant women and under the supervision of both an ophthalmologist and an obstetrician. Allergen immunotherapy is another option for severe symptoms and Immunotherapy is not initiated during pregnancy. Vasoconstrictor and decongestant eye drops are generally avoided during pregnancy [73].

### Allergic periocular dermatitis

If a contact allergy has been established as the cause of periocular dermatitis, the treatment of choice is to avoid the allergen.

In cases of atopic dermatitis, treatment is typically multimodal, involving topical therapies, emollients, treatment of infection if present, use of oral antihistamines for pruritus, and avoidance of triggering factors. Symptoms of atopic dermatitis involving the periocular tissues may be treated with calcineurin inhibitors [74].

In December 2000 topical tacrolimus ointment 0.03% was approved by the FDA for clinical use in moderate to severe AD for ages 2 years and up, with the higher strength 0.1% approved for ages 16 years and up. A year later, pimecrolimus was approved for mild and moderate atopic dermatitis for ages 2 years and up. Numerous studies have demonstrated their efficacy in atopic dermatitis [74]. Evidence-based confirmation of the safety of topical calcineurin inhibitors in the treatment of atopic dermatitis involving the face has been established in the literature [75].

Although the only approved indication for calcineurin inhibitors is treatment of atopic dermatitis, a number of placebo-controlled and open studies have shown the effectiveness of topical calcineurin inhibitors in the treatment of periorbital contact dermatitis, irritant contact dermatitis, seborrheic dermatitis, rosacea, facial, and intertriginous psoriasis vulgaris [76-78].

### Future Perspective

With increasing knowledge and advance in medicine engineering technology, the future of many disorders including ocular allergy is expected to change in a better direction. Given the pivotal role of IgE in the allergic cascade, antibodies directed against IgE or other allergic mediators represent the future therapeutic approach to allergic conjunctivitis. A relatively new and promising drug that is being introduced into the ocular allergy clinical practice with encouraging results include the recombinant humanized monoclonal antibody Omalizumab.

Omalizumab, an anti IgE antibody, is successfully used for the treatment of IgE mediated allergic disorders including persistent atopic asthma, atopic dermatitis, urticaria, eosinophil-associated gastrointestinal diseases and seasonal rhinoconjunctivitis [79,80].

Despite the lack of randomized clinical trials studying this drug in ocular allergy, few case reports showed omalizumab to be an effective and promising drug in the in the treatment of severe ocular allergy [79,81]. The lack of evidence based medicine on the use of these drugs in cases of ocular allergy, make it very difficult to agree on guidelines and recommendations for using these drugs. Clinical trial evaluating the efficacy and safety are required.

### Conclusion

Ocular allergy is a very common ocular inflammatory disorder with a significant impact on the quality of patient's life. Better understanding of the allergic mechanisms, inflammation, and classification helps physicians plan for and achieve the best treatment, thus the best control of symptoms. Some forms of ocular allergy can be controlled following simple life style modifications and traditional treatment delivered by a general ophthalmologist. However, some other forms of ocular

allergy are severe enough to require the collaboration of allergists and immunologists in order to achieve the best results.

In addition, the emergence of promising new therapies and medications for the treatment of nasal and ocular symptoms of allergy may change the future of ocular allergy treatment and improve the quality of life.

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