Allergic Eye Disease: Pathophysiology, Clinical Manifestations and Treatment

14

Bita Manzouri, Thomas Flynn, Santa Jeremy Ono

Core Messages

- Allergic eye disease affects a reported 20% of the population worldwide and may be increasing in line with other atopic diseases, such as asthma, as a result of environmental factors
- Other pathological mechanisms, in addition to the standard type I hypersensitivity reaction, have been recently implicated in the pathogenesis of allergic eye disease
- Established treatments have targeted mast cells, but as a result of our greater understanding of the mechanisms involved in eye allergy, researchers are now concentrating on other cell types, such as eosinophils and dendritic cells, as potential targets for immunomodulation
- Other areas of investigation to elucidate novel treatment strategies include the study of the genetics of ocular allergy, the role of environmental factors in the pathogenesis of ocular allergy, and the use of immunostimulatory DNA sequences that can inhibit the allergic response

14.1 Introduction

Owing to the fact that the eye is one of the first organs to encounter environmental allergens, allergic eye disease has become a common ocular problem, estimated to affect about 20% of the population worldwide [51]. Allergic eye disease is one of a spectrum of diseases that share a common initiating mechanism and pattern of inflammation and is a problem that is widespread among individuals who suffer with allergies. Although the incidence of allergic eye disease varies by geographical location, its prevalence is difficult to gauge as allergies tend to be underreported. A recent survey conducted by the American College of Allergy, Asthma and Immunology found that 35% of families interviewed in the United States experienced allergies, 50% of whom reported associated eye symptoms [48]. However, this prevalence is set to increase probably as a result of environmental factors. For example, the morbidity and mortality of asthma have increased with this, coinciding with the increase in house dust mite levels, and are greatest in communities exposed to high allergen levels [32].

Geographical variations, the lack of any clear-cut objective diagnostic criteria and the difficulty over the diagnosis – especially when it is the sole manifestation of atopy – have made it difficult to report the incidence rates for different forms of allergic eye disease. In the past, clinical features were used to classify allergic eye disease, but recent work that has defined the underlying pathogenic mechanisms has provided an understanding of the cellular and mediator mechanisms involved, thereby enabling a better understanding of the disease process and the development of more effective treatments.

Allergic conjunctivitis is typically divided into five types: seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis (GPC). The latter is an iatrogenic disease associated with foreign bodies on the eye, such as contact lenses and ocular prostheses.

Although not always included in this grouping, it is thought to have a possible allergic mechanism because of the predominance of mast cells. GPC invariably resolves when the cause is removed and keratopathy is rare.

The aim of this review will be to focus on the underlying mechanisms of allergic eye disease and the current classification of the various disease manifestations. Treatment modalities, both well established and new innovations, will also be discussed.

14.2 Pathophysiology

Ocular allergic disease is typically associated with immunoglobulin E mediated mast cell activation (type I immediate hypersensitivity reaction) in the conjunctival tissue. However, recent data from several groups indicate that other additional mechanisms can also be involved in causing a red, allergic eye.

14.2.1 Type I Hypersensitivity

The allergic response begins when allergen is encountered by an antigen presenting cell (APC), either directly or as part of an immune complex with immunoglobulin. The APCs then process and present the allergen to CD4+ T cells as a peptide fragment in association with the major histocompatibility (MHC) class II molecule. These T cells are then polarized into T helper type 1 (Th1) cells and T helper type 2 (Th2) cells. The Th2 cells produce a variety of interleukins, two of which – IL-4 and IL-13 – stimulate immunoglobulin class switching of B cells from producing IgM to producing IgE. This immunoglobulin binds to high affinity receptors (FceRI) on the surface of mast cells and basophils. Subsequent encounter with this allergen results in the cross linkage of IgE bound to FceRI on the surface of mast cells and a cascade of signal transduction with a resultant release of preformed and newly synthesized mediators. Tissue fibroblasts and epithelial cells are also triggered by Th2 cells to produce chemokines such as monocyte chemoattractant protein-1 (MCP-1), eotaxin-1, or the protein regulated on activation normal T-cell expressed and secreted (RANTES), resulting in the migration of inflammatory cells into the site of allergen exposure [5].

This sensitized mast cell mediated response is responsible for many of the symptoms seen in SAC and PAC – such as itching, redness and eyelid swelling – with most of these patients having a positive family history of atopy and raised levels of allergen specific IgE in the serum and tears [32]. Immunohistochemical studies have shown that in SAC there is a significant increase in the numbers of conjunctival mast cells, which correlates with the patient's severity of symptoms [32]. A number of proinflammatory cytokines are released by mast cells and these include histamine, leukotriene C_4, prostaglandin D_2, platelet-activating factor (PAF), tryptase, chymase, cathepsin G and other eosinophil and neutrophil chemoattractants in what is termed the early phase response [32]. This response lasts for a maximum of 20 min after allergen activation and includes enhanced tear levels of histamine, protease tryptase, and leukotrienes, and an increase in the number of eosinophils [46]. At about 6 h a late phase response occurs which includes a second peak of tear histamine (without an increase in tryptase) and an increase in tissue adhesion molecules E-selectin and interstitial cell adhesion molecule 1 (ICAM-1), which is followed by an influx of inflammatory cells such as neutrophils, T cells, basophils and eosinophils [46]. The presence of tear histamine and the absence of tear tryptase in the late phase response may indicate that basophils, as opposed to mast cells, are involved.

Mast cells are also known to synthesize, store and release a number of cytokines such as IL-4, IL-5, IL-8, IL-13 and TNFα [46]. Cytokine involvement, particularly the Th2 cytokines, has been the focus of many studies recently looking into the mechanisms of ocular allergy. It is known, for example, that IL-4 plays a key role in allergic inflammation by promoting T-cell growth, by inducing the production of IgE from B cells, by upregulating the adhesion molecule vascular cell adhesion molecule 1 (VCAM 1), and by regulating the differentiation of the Th2

subset, which is essential for the allergic reaction [19, 31].

Physiologically, mast cells represent a heterogeneous population. They are subdivided on the basis of their ultrastructural characteristics, protease content, and T-lymphocyte dependency [49]. In humans, mast cells that contain tryptases, chymases, carboxypeptidase A, and cathepsin G are designated MC_{TC} and those that contain tryptase only are designated MC_T. Although both subtypes develop from the same CD34+ mononuclear precursor, the MC_T subtype is dependent on the presence of T lymphocytes, present at mucosal surfaces, and increases in number in aeroallergen driven allergic disease, whilst the MC_{TC} subtype appears to be independent of T cells but its development requires fibroblastic derived growth factors, which are predominant in connective and perivascular tissues, and is characteristic of fibrotic processes [32]. Normally, approximately 80 % of conjunctival mast cells are of the MC_{TC} phenotype and are mainly subepithelial in distribution, with the rest being MC_T, but during allergic inflammation such as that seen in SAC, VKC or AKC, the numbers of the latter type increase in the epithelial and subepithelial layers [37]. In the chronic and fibrosing condition AKC, however, the MC_{TC} subtype predominates, perhaps indicating an important transition from a simple mediator driven disorder to that of chronic inflammation leading to conjunctival fibrosis [37].

14.2.2 Ocular Inflammatory Reaction: Late Phase

A late phase reaction sustained by a complex network of inflammatory cells and mediators can also occur in the eye. This has been demonstrated in humans using allergen for conjunctival provocation of allergic subjects [10]. Allergen challenge caused the typical early-phase reaction within 20 min, with the initial reaction being dose dependent. With smaller doses of allergen the reaction was not so pronounced and spontaneous recovery occurred within a brief period. With larger doses, the reaction was more persistent and progressed to a late-phase reaction. Typically, high doses of allergen induced a continuous reaction manifested by burning, redness, itching, tearing and a foreign body sensation that began 4–8 h after challenge and persisted for up to 24 h. This clinical reaction was accompanied by a significant recruitment of inflammatory cells in tears. Neutrophils first appeared about 20 min after challenge, with eosinophils and lymphocytes increasing in prominence 6–24 h after challenge.

The eosinophil predominates in the late phase reaction. It is a powerful effector cell, releasing arginine rich toxic proteins capable of causing corneal epithelial damage [32]. Normally, eosinophils are not found in the conjunctival epithelium of non-atopic subjects but the numbers are increased in the conjunctival epithelium, subepithelium and tears of patients with AKC and, to a greater extent, VKC patients. Furthermore, this increase in eosinophils and eosinophil products [e.g. eosinophil peroxidase, eosinophil cationic protein (ECP)] is also present in both skin test positive and skin test negative VKC and is not confined to ocular tissues. This suggests that, in at least some forms of allergic conjunctivitis such as VKC, eosinophilic infiltration – and not IgE sensitization – is the more relevant feature of the disease and is associated with signs of systemic activation of eosinophils [10].

14.2.3 Non-specific Conjunctival Hyperreactivity

Non-specific stimuli can also cause target organ hyperreactivity and this is thought to play a role in allergic diseases of the eye. It is postulated that "non-specific conjunctival hyperreactivity" may represent a distinct pathophysiological abnormality in allergic eye disease [10]. The variability of symptoms experienced in allergic conjunctivitis which do not correlate with environmental changes such as the levels of sensitizing allergens, as well as the ocular reaction induced by non-sensitizing stimuli, may well be explained by this non-specific hyperreactivity. Natural non-specific stimulation with agents such as wind, dust, and sunlight may act only as

triggers of an abnormal non-specific reactivity of the conjunctiva in allergic patients [10].

Furthermore, multiple physical, chemical, infectious, or antigenic factors may stimulate the biological responses of mast cells, leading to the release of several mediators. Rubbing of the eyes, exposure to UV light, and increase of ocular surface temperature may lead to acute degranulation of the mast cells and release of their mediators. The local generation of stimuli that induce different patterns of mast cell cytokine release may represent another method of biological, non-specific activation of mast cells [42]. It has been observed that whenever a patient with VKC is exposed to the sun, signs and symptoms recur. Furthermore, the symptoms of allergy become most severe in children with VKC who develop bacterial conjunctivitis. Certain types of lipopolysaccharides of bacteria may cause degranulation of mast cells, leading to the release of their mediators that cause exacerbation of the allergic process.

14.2.4 T-Cell-Mediated Hypersensitivity in Allergic Eye Disease

Both CD4+ and CD8+ T cells populate the subepithelial tissue of the normal human conjunctiva. In the active forms of SAC and PAC, the T cell profile remains virtually unchanged compared to the normal milieu, but in chronic allergic disorders such as VKC, AKC and GPC, CD4+ T cells but not CD8+ T cell numbers are increased, with a mixed cellular infiltrate containing many mast cells, eosinophils, neutrophils, and macrophages [32]. In chronic allergic diseases there is no clear-cut difference between the allergen specific IgE responses and the nature and severity of the allergic responses; hence it is likely that non-IgE mechanisms are contributory, with the involvement of cell mediated responses [32].

Most of the T cells in normal conjunctiva are naïve, but in chronic allergic conditions 90 % of the T cells are memory T cells [35]. Corresponding with this rise in activated T cells, there is also upregulation of markers present on antigen presenting cells.

CD4+ T cells can be further subdivided into two distinct subsets based on their pattern of cytokine production. The first subset, Th1 cells, produce IL-2, IL-3, TNFβ and interferon γ (IFNγ) and are more associated with classic delayed type hypersensitivity. The second subset, Th2 cells, produce a range of cytokines encoded on chromosome 5, such as IL-4 and IL-5, which promote immediate hypersensitivity responses through their ability to stimulate proliferation, B cell IgE production and eosinophil production, activation and survival [32]. It has been shown that in AKC there is increased numbers of both Th1 and Th2 lymphocytes as opposed to in VKC where lymphocytes secreting cytokines typical of the Th2 subset are found. This observation suggests that VKC results from a maturation shift of CD4+ T cells towards a pattern of secretion of cytokines which drives a mast cell and eosinophil mediated inflammatory response [34].

14.3 Clinical Syndromes of Allergic Eye Disease

Allergic diseases of the eye comprise a number of different inflammatory conditions that share common features such as seasonal variation, association with atopic disease and presumed involvement, to a greater or lesser extent, of the type I hypersensitivity mechanism in their pathophysiology. They are traditionally classified, as outlined above, into five distinct entities: SAC, PAC, VKC, AKC, and GPC (Fig. 14.1).

As previously mentioned, recent evidence suggests that the traditional type I hypersensitivity reaction may be less important in some of these diseases than others. However, these diseases share many symptoms in common and it is therefore reasonable to group them in the same broad category of "allergic eye disease". The cardinal feature of all allergic eye disease is itching – in the absence of this symptom one should be wary of making this diagnosis. Other symptoms such as tearing, burning and foreign body sensation may be present in variable degrees in all of these conditions. Despite similarities in the symptoms, it is important to distinguish, where possible, between the different

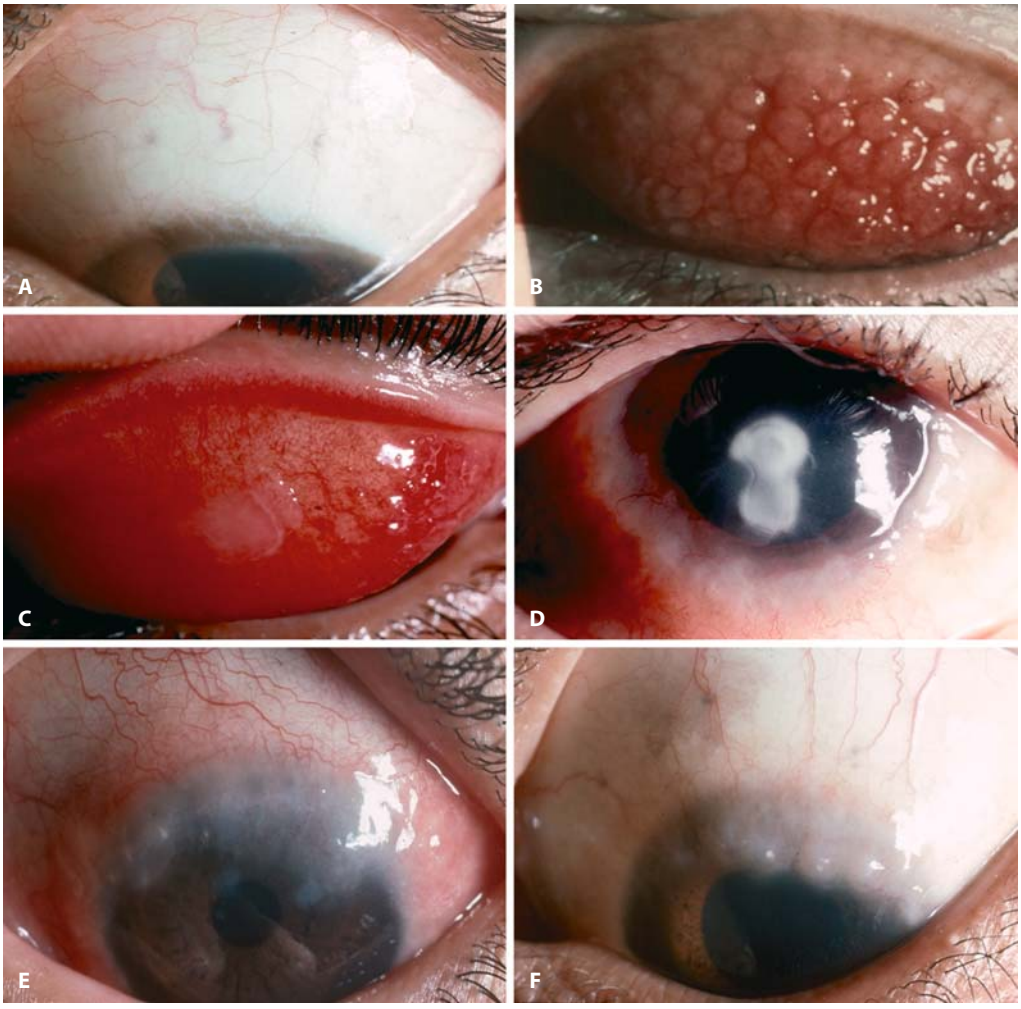

Fig. 14.1. **A** Normal bulbar conjunctiva; **B** giant papillae in GPC; **C** typical appearance of superior tarsal conjunctiva in a severe case of SAC; **D** corneal ulcer in VKC; **E** early stages of corneal pannus in AKC; **F** Horner-Trantas dots seen in AKC. (Pictures courtesy of Dr. Mohammed Siddique, Institute of Ophthalmology, London)

types of allergic eye disease as each of them has a different visual prognosis. Accurate diagnosis will allow appropriate counselling of patients.

The most common type of allergic eye disease, seasonal allergic conjunctivitis (hay fever conjunctivitis), is also the least serious in terms of visual outcome. SAC and PAC together account for 98 % of allergic eye disease [41]. VKC and AKC, although much rarer, are more likely to lead to visual impairment, with AKC being the most destructive disease and having the worst visual prognosis. The emergence of newer treatments based on an increasing understanding of the individual pathogenic mechanisms of each disease also underlines the importance of accurate diagnosis. The different types of allergic eye disease can usually be distinguished by history and examination alone.

14.3.1 Seasonal Allergic Conjunctivitis

Of the allergic eye diseases, SAC represents the most "pure" form of type I hypersensitivity. As the name suggests, the symptoms and signs are intermittent and occur rapidly following exposure to a specific allergen, with patients often having a personal or family history of atopy. In the absence of prolonged exposure to allergen, attacks are short lived. The commonest seasonal allergen is pollen, with tree pollen predominating in spring, grass pollen in summer and ragweed pollen in autumn. Symptoms are typically absent during winter. The severity of signs and symptoms varies from patient to patient depending on the specific allergen and the exposure.

14.3.1.1 Symptoms

Patients usually complain of intense itching of the eyes associated with a watery discharge.

14.3.1.2 Signs

There may be eyelid oedema. Conjunctival vessels may be injected and conjunctival chemosis may give the conjunctiva a "milky" appearance. Symptoms and signs are usually bilateral although they may be asymmetrical. Young children can present with dramatic unilateral lid oedema and chemosis.

14.3.2 Perennial Allergic Conjunctivitis

PAC is less common than SAC. Although the symptoms and signs of these diseases are the same, the distinction between them lies in the timing of the symptoms. Whereas SAC sufferers have symptoms for a defined period of time, PAC sufferers are sensitive to allergens that are present year-round and so are perennially symptomatic. "Household" allergens such as the dust mite or pet dander are the usual offenders in PAC. These patients may also be sensitive to seasonal allergens and so there may be a superimposed seasonal element to their symptoms.

14.3.3 Vernal Keratoconjunctivitis

A disease of childhood, VKC accounts for 0.5 % of allergic eye disease [32]. Like AKC it has a male preponderance but onset is much earlier, typically late in the first decade. It is seen most commonly in temperate climates such as those of the Mediterranean, South Africa and North America. However, genetic as well as environmental factors are important. Even in cooler northern climates the disease is more commonly seen in people of African or Asian descent [39]. There is frequently a personal or family history of atopy but this association is not as strong as in other types of allergic eye disease, with a large proportion of VKC patients having no such history.

In the majority of cases the disease shows seasonal variation with symptoms typically appearing in spring and lasting about 6 months. Additional recurrences in winter are common. In some cases the disease evolves over time into a more chronic, perennial form of inflammation with up to one-quarter of VKC patients having a perennial form of the disease from the outset [11]. Although serious visual complications may occur, VKC is a less destructive disease than AKC and usually burns itself out by the early twenties [30].

14.3.3.1 Symptoms

Symptoms are usually bilateral but may be asymmetrical and, like all allergic eye diseases, itching is a cardinal feature. Photophobia is also prominent and patients may complain of tearing and a mucoid discharge. Depending on the severity of corneal involvement, they may also complain of a foreign body sensation or pain.

14.3.3.2 Signs

In contrast to AKC, the periorbital skin is usually unaffected. The disease is further classified into tarsal, limbal or mixed VKC depending on the location of the conjunctival inflammatory signs.

Tarsal. The inflammation is predominantly in the superior tarsal conjunctiva although the bulbar conjunctiva may show non-specific signs such as injection or chemosis. The superior tarsal conjunctiva develops a papillary reaction. Papillae are typically large (>1 mm) and diffuse, giving a "cobblestone" appearance. These tarsal papillae tend to persist even when the disease is quiescent but become hyperaemic and oedematous during periods of disease activity. The presence of a thick, mucoid, white secretion associated with these papillae is another indicator of disease activity. Papillae may enlarge to several millimetres in diameter and may give rise to ptosis. In severe forms of the disease, linear subepithelial scars (Arlt's lines) may appear parallel to the lid margin.

Limbal. Limbal VKC is characterized by single or multiple gelatinous, pale infiltrates in the limbal conjunctiva. The extent of limbal involvement is variable. Infrequently, there may be 360° limbal inflammation. There is usually injection of the surrounding bulbar conjunctival vessels. Aggregates of degenerating eosinophils at the apex of the infiltrates are seen as small white spots (Horner-Trantas dots) – both the limbal infiltrate and the Horner-Trantas dots are transient.

In mixed VKC both limbal and tarsal signs may be observed. Although limbal and tarsal VKC are believed to be variants of the same disease, certain differences have been observed in their demographics and natural history. Limbal VKC is particularly common in people of African or Asian descent. There is mixed evidence as to which, if either, of the variants is more responsive to treatment [11, 52]. Patients with tarsal disease are certainly more likely to develop sight-threatening corneal ulceration [52].

Cornea. Sight-threatening complications occur less frequently in the cornea than in AKC. However, both non-specific and pathognomonic corneal signs are seen. In a follow-up series of 195 patients with VKC, 9.7% developed corneal ulcers and 6% developed a permanent decrease in visual acuity [11]. Abnormalities of the central and superior cornea are most commonly seen in tarsal disease. In its earliest form there may be only punctuate epithelial erosions. These may, with time, coalesce to form larger erosions that may in turn evolve into the characteristic "shield" ulcer of VKC. Shield ulcers are non-infectious and occur in the central/superior cornea. At first they are shallow with a transparent base. Over time the ulcer becomes filled with inflammatory debris and the base opacifies. Further accumulation of inflammatory debris leads to plaque formation. The pathogenesis of these ulcers is incompletely understood. Mechanical abrasion of the epithelium by large papillae on the superior tarsal conjunctiva is thought to play a role, as is epithelial corrosion by toxic granule proteins released from eosinophils in the tarsal conjunctiva and tear film. In persistent or recurrent limbal disease, peripheral corneal signs such as pannus or opacification (pseudogerontoxon) may develop. Limbal lesions may also cause significant astigmatism.

14.3.4 Atopic Keratoconjunctivitis

First described in 1952 [22], AKC constitutes a more relentless form of conjunctival inflammation than either SAC or VKC. Atopic dermatitis (eczema), a pruritic skin condition that affects 3% of the population, is present in 95% of patients with AKC [7]. Conversely, 25–40% of atopic dermatitis patients have AKC [18]. Typically patients have had atopic dermatitis since childhood with ocular symptoms developing at a later stage. Symptoms may begin in the late teens or early twenties but the peak incidence is between the ages of 30 and 50. Males are more commonly affected than females and there is often a personal or family history of other atopic diseases. Unlike SAC, and most cases of VKC, the symptoms are perennial. It differs from PAC in

that the symptoms are less intermittent. Although there may be periods of relative quiescence, signs of disease activity are usually present to some degree.

14.3.4.1 Symptoms

Bilateral itching of the eyelids and periorbital skin is the most frequent symptom. Patients also complain of tearing, photophobia, burning and blurred vision. Increased mucus and inflammatory debris may thicken the tear film and contribute to a stringy discharge. Depending on the severity of corneal involvement, patients may complain of a foreign body sensation and pain.

14.3.4.2 Signs

Invariably there are signs of disease on the eyelids and periorbital skin. Ocular surface inflammation in AKC may, as the name suggests, affect the conjunctiva and cornea. In many cases the disease is mild and corneal signs may actually be absent or minimal. Such cases have been termed atopic blepharoconjunctivitis (ABC) [53].

Eyelids. The periorbital skin typically has the dry, indurated and scaly appearance of eczema. Eyelid swelling may contribute to the generalized wrinkling of the skin and the development of a fold in the lower lid skin (Dennie-Morgan fold). In severe cases there may be fissures at the lateral canthus and/or absence of the lateral part of the eyebrow (Herthoge's sign). The latter signs may be induced or aggravated by vigorous eyelid rubbing. Lid margins may be thickened (tylosis) and may develop meibomian gland dysfunction. Colonization of the lid margin with staphylococcus with resultant staphylococcal blepharitis is common [54].

Conjunctiva. There is typically a papillary reaction on the tarsal conjunctiva, which, in contrast to VKC, is usually more prominent on the inferior, rather than the superior, tarsal conjunctiva. The bulbar conjunctiva may show non-specific signs of inflammation such as hyperaemia or chemosis. Rarely, papillary hyperplasia of the limbal conjunctiva occurs, resulting in a gelatinous limbal nodule similar to those seen in limbal VKC. Associated Horner-Trantas dots have been seen. Prolonged or severe inflammation may result in conjunctival cicatrization. This is most commonly seen in the lower fornix and may result in shallowing of the fornix and symblepharon. Activation of fibroblasts by mast cells has been proposed as a mechanism for conjunctival scarring in allergic disease [47]. Several cases of squamous cell carcinoma/CIN have been reported in patients with atopic dermatitis or AKC [20, 24] although the mechanism of tumourigenesis remains unclear.

Cornea. Visual deterioration in AKC is most commonly caused by corneal complications. Corneal scarring in AKC may result from vascularization, infection or keratoconus. A broad spectrum of corneal disease may be seen depending on the severity and chronicity of inflammation. Punctate epithelial erosions are seen early in the course of the disease. The severity of the corneal erosions correlates with the number of inflammatory cells (especially eosinophils) in brush cytology samples from the superior tarsal conjunctiva [50]. Peripheral corneal vascularization, which may be associated with opacification, is common. These changes may occur as a result of limbal stem cell deficiency. Rarely, corneal vascularization may encroach on the visual axis and cause visual impairment. Epithelial erosion may coalesce to form non-infectious corneal ulcers. Toxic granule proteins derived from conjunctival eosinophils have been implicated in the pathogenesis of these ulcers [33]. Staphylococcal colonization of the lid margins coupled with a decrease in barrier function [56] also puts AKC patients at increased risk of developing bacterial infectious corneal ulcers. They are particularly vulnerable to herpes simplex keratitis [16]. Chronic eye rubbing may be an important factor in the association between AKC and keratoconus [6].

Other Causes of Visual Deterioration in AKC. AKC is associated with the development of premature bilateral cataracts. Typically the lens

opacity develops in the anterior subcapsular region and has well defined margins. It is often referred to as a "shield" cataract. A rarer cause of visual impairment in AKC is that of retinal detachment [57]. The reasons for this association are not well understood. Finally, chronic use of topical steroids in the treatment of AKC may result in posterior subcapsular cataracts and glaucoma (see below).

14.3.5 Giant Papillary Conjunctivitis

The term giant papillary conjunctivitis describes the advanced stages of the conjunctival response to the prolonged presence of a foreign body on the ocular surface. It was first observed and characterized in contact lens wearers [3] and was later reported in patients with ocular prostheses and exposed suture ends. Nowadays, it is seen commonly in contact lens wearers, and most of the knowledge of this condition arises from experience with these patients. Wearers of soft contact lenses are most likely to develop giant papillary conjunctivitis, but it has been estimated that 1–5 % of rigid gas-permeable lens wearers may also be affected [26, 27]. The condition shows no age or gender preference and there does not appear to be a strong association with allergy [28].

14.3.5.1 Symptoms

Earliest symptoms are of mucus discharge in the morning and itching on removal of the lenses. As the disease progresses these symptoms become more marked and may be associated with a foreign body sensation. Patients complain of blurred vision as a result of coating of the lens with mucus and increasing lens mobility and instability. As the disease advances patients become increasingly intolerant of their contact lenses.

14.3.5.2 Signs

Giant papillary conjunctivitis is characterized, in the late stages, by the presence of abnormally large (>0.3 mm) papillae on the superior tarsal conjunctiva. In the earliest stage, however, when the patient first becomes symptomatic, the conjunctiva may appear normal. As the disease progresses the superior tarsal conjunctiva becomes thickened and hyperaemic. Small papillae develop first which increase in size and number over time. The distribution of giant papillae varies according to the type of lens worn. In wearers of soft lenses papillae emerge first at the superior edge of the tarsal plate. Wearers of hard lenses, which are smaller, develop papillae closer to the superior lid margin [23]. The bulbar conjunctiva and inferior fornix are usually normal.

The symptoms and signs of this disease may resemble those of VKC. Important factors in the history, which could help to distinguish these conditions, include contact lens history and patient age since VKC is seldom seen after the early twenties.

14.4 Treatment of Allergic Eye Disease

The mainstays of treatment for the majority of allergic eye disease symptoms are topical eye drops, and for this purpose a wide range of topically administered agents have been developed to treat the milder disease varieties. These include antihistamines, mast cell stabilizing agents and anti-inflammatory agents. Additionally, topical nasal decongestants are also available. Of the topical eye drops, it is antihistamines and mast cell stabilizers that have been extensively studied to assess their therapeutic value in a large number of comparative clinical trials over the years. Furthermore, as the chemical and cellular infiltrates in both acute and chronic allergic eye disease become better characterized, there are significant implications for treatment of these conditions. Efficacy of all of these agents varies from patient to patient and the choice of agent used depends on a number

of variables, such as the underlying state of health of the eye being treated, drug costs and availability, contact lens wear, and the potential for compliance [8].

The preferred treatment modality in mild diseases such as SAC and PAC is topical therapy, since neither is sight threatening, and their pathogenesis involves mast cell degranulation and the release of histamine. Topical treatment offers several advantages: the ease of application directly to the site affected by the disease process, the general lack of systemic side effects, and the washout effect of the drops themselves aiding the removal of the inflammatory mediators.

14.4.1 Antihistamines

The first line of treatment of ocular allergy includes the avoidance of allergens, the use of cold compresses for symptom relief (especially itching), and regular lubrication of the eye to wash out tear histamine and other inflammatory mediators, thus diluting their effects and aiding the patient's comfort. Topical therapy may start with the use of antihistamines or mast cell stabilizers. Considering the former, the stimulation of H1 receptors in the conjunctiva mediates the symptom of itching whereas H2 receptor activation results in vasodilation. Second generation H1 receptor antagonists are used for the topical treatment of the benign forms of allergic conjunctivitis, and these include levocabastine, azelastine and emedastine. They all bind selectively to H1 receptors in the conjunctiva and have little or no effect on dopaminergic, adrenergic or sertotoninergic receptors [46]. Of this new generation H1 receptor antagonists, topical azelastine has been shown to be a powerful topical antihistamine, decreasing eosinophil and T lymphocyte activation, having an inhibitory effect on a broad array of other mediators, and being a potent suppressor of itching and conjunctival hyperaemia after conjunctival provocation with an allergen, with an onset of action seen within 3 min and a duration of effect of at least 8–10 h [32, 46]. Although topical antihistamines can be used alone to treat allergic conjunctivitis, combining an antihistamine with a vasoconstrictor is more effective than either agent alone. The vasoconstrictors commonly used in combination with topical antihistamines are phenylephrine or naphazoline [8].

14.4.2 Mast Cell Stabilizing Agents

The most common topical drugs invariably used by ophthalmologists for all forms of allergic conjunctivitis are the mast cell stabilizing agents. These include sodium cromoglygate, lodoxamide, ketotifen, nedocromil sodium and the newly introduced olopatadine. Mast cell stabilizers are effective in the milder forms of allergic eye disease and have very few side effects, either locally or systemically, but for patients to receive long-term benefit from them such that expected exposure to allergen reduces the tryptase and inflammatory cells after allergen challenge, treatment is needed for many years [46].

Sodium cromoglygate is the prototypic mast cell secretion inhibitor. It is the oldest and most widely used agent of this family of drugs. However, despite its extensive use, the mechanisms of its action are still unclear. The efficacy of the medication appears to be dependent on the concentration of the solution used [9]. Nedocromil sodium has been shown to be able to inhibit chloride ion flux in mast cells, epithelial cells and neurons. This feature may explain how it can prevent responses such as mast cell degranulation. Others have suggested the inhibition of IgE production by B cells as an alternative mechanism [46]. Newer agents such as lodoxamide have become available, which are faster acting and approximately 2,500 times more potent than sodium cromoglycate in the prevention of histamine release, that also act to reduce tear tryptase and inflammatory cells after allergen challenge [8]. In a comparative trial with sodium cromoglygate and lodoxamide in subjects with the more severe forms of allergic eye disease (VKC, AKC and GPC), lodaxamide was found to be superior for symptom relief. It was also found to be effective in the long-term

treatment of VKC especially in cases with an epitheliopathy [17, 43].

14.4.3 Dual-Acting Agents

Dual-acting agents are named for their antihistamine effects and their inhibition of mediator release. They are the newest generation of antiallergic agents. The advantages of these drugs lie in 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 of these agents are equivalent and in selecting a dual-action agent, one should look for a potent and long-lasting agent that relieves the signs and symptoms of allergy, including itching, redness, lid swelling and chemosis [41].

Clinical studies have demonstrated the efficacy and tolerance of olopatadine for the management of allergic conjunctivitis or in a conjunctival allergen model [1, 4, 13]. This agent both acts as a mast cell stabilizer and has antihistamine activity. This dual mode of action has been shown to be advantageous for the management of allergic conjunctivitis, and as a topical preparation has been subjectively preferred by patients [4, 44]. Furthermore, a direct anti-inflammatory property for this drug has been suggested by a study which showed that olopatadine inhibited the anti-IgE antibody-mediated release of TNFα from human conjunctival mast cells [14].

14.4.4 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Prostaglandins, especially PGE_2 and PGI2, lower the threshold of the human skin and conjunctiva to histamine-induced itching. NSAIDs, by inhibiting the production of prostaglandins, help to alleviate this itching but also reduce pain and inflammation of the eye associated with allergic reactions [9, 46]. NSAIDs used in the topical treatment of allergic ocular conditions include ketorolac, diclofenac, fluribrofen and indomethacin. These agents, unlike corticosteroids, do not mask ocular infections, affect wound healing, increase intraocular pressure, or contribute to cataract formation [8]. However, of these agents, only ketorolac tromethamine (Acular) has been approved by the Food and Drug Administration for the management of acute SAC [15]. It acts to significantly reduce tear tryptase levels and the number of eosinophils and lymphocytes in tear specimens after conjunctival provocation [29].

Ocular NSAIDs have been associated with a low-to-moderate incidence of burning and stinging [9]. The concern of NSAID-induced asthma does not appear to be a problem except in patients who have the triad of asthma, nasal polyposis and aspirin sensitivity [45].

14.4.5 Topical Corticosteroids

Topical steroid preparations are the most effective therapy for moderate to severe forms of VKC, but their use should be strictly limited for severe cases and carefully monitored since their long-term use is associated with an increased risk for the development of cataracts and glaucoma and can potentiate ocular herpetic infections. In fact, topical steroids are responsible for the 2% incidence of glaucoma in VKC patients [12]. In T cell dependent AKC and VKC, sodium cromoglycate has been used either prophylactically or as maintenance therapy to control mild symptoms only, but is ineffective in acute exacerbations. In acute exacerbations, even the newer class of mast cell stabilizers may not be enough, and under these circumstances steroids (fluoromethalone or dexamethasone) tend to be used in doses of up to one drop hourly to reverse corneal epitheliopathy caused by the release of epithelial toxic mediators from eosinophils and neutrophils [32]. Once control of the acute phase of the disease has been achieved, steroids should be discontinued and alternative topical treatment, as outlined previously, should be started [12].

Two modified corticosteroids have recently been investigated for their efficacy in allergic conjunctivitis: rimexoline (a derivative of pred-

nisolone) that is quickly inactivated in the anterior chamber of the eye, thus improving efficacy and decreasing the safety concerns, e.g. raised intraocular pressure; and both low-dose and high-dose loteprednol etabonate are highly effective as prophylaxis against, and in the acute phase of, allergic conjunctivitis [8].

14.4.6 Calcineurin Inhibitors

Two calcineurin inhibitors are currently in clinical use:

1. Cyclosporin A (CsA) is a fungal antimetabolite and anti-CD4+ agent that decreases the clinical signs and symptoms of the chronic forms of VKC and AKC. It acts to control ocular inflammation by blocking Th2 lymphocyte proliferation and IL-2 production, by inhibiting histamine release from mast cells and basophils, and by reducing the production of IL-5, thereby reducing the recruitment and effects of eosinophils on the conjunctiva [12]. Although systemic CsA has been used for the treatment of severe AKC and keratoconjunctivitis sicca, topical cyclosporin causes ocular irritation with burning, tearing, erythema and itching. This is due to the fact that since the drug is lipophilic, it has to be dissolved in an alcohol base which causes the ocular irritation [8]. However, the topical form of this drug is not yet generally available.

   CsA has been evaluated in patients with steroid dependent AKC. In one study, 12 patients were randomized to treatment with CsA and 9 patients to a vehicle treatment group. The results showed that in the CsA group, 9 out of 12 patients were able to cease steroid therapy as compared to 1 out of 9 in the vehicle group [21]. Furthermore, the final steroid use was significantly lower in the CsA group versus the vehicle group. This study concluded that CsA is an effective and safe steroid sparing agent in AKC and is also capable of improving the symptoms and signs of AKC. In another randomized trial the short-term efficacy and safety of topical CsA 0.05% was evaluated in the treatment of patients with severe, steroid resistant AKC [2]. Patients were randomly assigned to treatment with topical CsA 0.05% or placebo for a period of 28 days with the symptoms and signs of AKC recorded on the day of enrollment and at the end of the treatment period. The results, recorded by a composite score computed by summing the severity grade of all five symptoms and six signs of AKC, showed a greater improvement in the CsA group relative to the placebo group at the end of the treatment period. It was hence concluded that topical CsA 0.05% is safe, and may actually have some effect in alleviating the signs and symptoms, in severe AKC that is resistant to topical steroid treatment.
2. Tacrolimus (FK-506) is a macrolide antibiotic with potent immunomodulatory properties which has already been used to treat the immune mediated problems encountered with corneal graft rejection, ocular pemphigoid and uveitis. It acts on T lymphocytes to block the production of lymphokines, such as IL-2, IL-2, IL-5, TNFα and interferon-γ a. It also blocks the degranulation of mast cells and several mast cell cytokines, such as IL-3 and IL-5 [8].

14.4.7 Future Drug Developments

The aims of future drug development will focus on steroid-sparing agents that control the immune response. These may be administered alone, or in combination with newer drugs that have already demonstrated their efficacy in the management of these conditions, such as antihistamines and mast cell stabilizers.

Our understanding of the pathophysiology of allergic conjunctivitis has increased greatly over the last 3 years. New areas of investigation to elucidate novel treatment strategies include the study of the genetics of ocular allergy, since it has been known for some time that different mouse strains are more or less responsive to specific allergen challenge in the eye, and linkage analysis of these mice is being pursued to define disease susceptibility genes for ocular allergy [41]. A few studies have addressed the

role of environmental factors in the pathogenesis of ocular allergy. For example, it has been shown that there is a positive association between the dietary intake of n-6 polyunsaturated fatty acids and seasonal allergic rhinoconjunctivitis [55]. Other studies have focused on the genetics of allergic conjunctivitis. One of the earliest published studied approximately 117 families with probands with allergic conjunctivitis [40]. Evidence was found, by analysis of the genomic DNA, for genetic linkage of allergic conjunctivitis for chromosomes 5, 16 and 17. This genetic linkage for allergic conjunctivitis was shown to differ from that reported for atopic asthma, and hence it was concluded that there were likely to be organ specific disease susceptibility genes, which, together with general atopy genes, target the allergic response to specific mucosal tissues.

Resident dendritic cells in the conjunctiva have also been the focus of recent research since it has been shown that dendritic cell activation by an allergen is a very early step in disease pathogenesis, with dermal allergy being used as the prototype [41]. Other areas of interest lie in the activation and mediator release from human conjunctival mast cells on FceRI cross-linking. A recombinant humanized monoclonal anti-IgE antibody, omalizumab, was recently developed which binds specifically to the IgE binding site on human FceRI and thereby blocks the binding of IgE to mast cells and basophils [5]. Studies have shown that this agent benefits patients with moderate to severe allergic asthma who remain symptomatic despite treatment with systemic or inhaled corticosteroids [5]. Additionally, omalizumab has been shown to be safe and well tolerated.

One of the most innovative treatment advances has been in the use of immunostimulatory DNA sequences that can inhibit the allergic response. Both bacterial DNA and synthetic oligodeoxynucleotides containing specific motifs centered on a CpG dinucleotide have been shown to be potent immunostimulatory agents [46]. It is likely that these sequences represent a signal to the immune system, resulting in a powerful Th1 response and this can be used to switch an allergic response from a Th2 dominated immune profile towards a Th1 profile [46]. Miyazaki et al. evaluated the therapeutic potential of immunostimulatory sequence oligodeoxynucleotide (ISS-ODN) administration in ocular allergy using a mouse model of ragweed-specific conjunctivitis [36]. They concluded that ISS-ODN was an effective treatment for ocular allergy when administered systemically or conjunctivally. Systemic treatment markedly inhibited clinical parameters of SAC and blocked conjunctival eosinophilia in the late phase reaction. Additionally, it also effectively blocked neutrophilia, which is a hallmark of the late phase reaction.

Other areas of potential therapeutic value which require further research include the use of antagonists of the action of macrophage inflammatory protein-1α (MIP-1α) and the use of IL-1 receptor antagonists. Data have shown that MIP-1α constitutes an important second signal for mast cell degranulation in the conjunctiva in vivo and consequently for acute phase disease [38]. Therefore, antagonizing the interaction of MIP-1α with its receptor (CCR1) or signal transduction from this receptor may hold promise for future treatment of both acute and late phase reactions. Similarly, in a mouse model of allergic eye disease, IL-1 inhibition using an IL-1 receptor antagonist was found to downregulate the recruitment of eosinophils and inflammatory cells by decreasing the concentration of attractant chemokines [25]. This research also offers a potential novel treatment for the prevention and treatment of allergic eye disease.

14.5 Conclusion

Allergic eye disease represents a heterogeneous group of diseases that share a common symptomology but different pathogenesis. They are further distinguished by their long-term visual prognosis, with diseases such as SAC and PAC having no long-term effects on sight whereas VKC and AKC, through corneal involvement and subsequent scarring reactions, can adversely affect visual prognosis. Future work needs to increase our understanding of the genetics and mechanisms of mast cell cytokine expression and mediator release, the regulation of the

cellular inflammatory response and the B cell regulation of IgE secretion. Armed with this knowledge, more ways of treating allergic eye disease will be developed which will target more specific components of the allergic response. Most novel therapies so far have been directed at controlling the allergic response in the bronchial airways and the nasal mucosa, but it is hoped that new strategies will begin to focus treatment on ocular disease to downregulate the allergic response rather than to control its effects.

Summary for the Clinician

- **Allergic eye disease is a common problem. It is reported to affect about 20% of the population worldwide but this may be an underestimate of the true prevalence of the condition due to geographical variations and the lack of any clear cut objective diagnostic criteria**
- **There are five main syndromes of allergic eye disease, two of which (vernal and atopic keratoconjunctivitis) have sight-threatening complications; hence it is important to strive to make an accurate diagnosis due to the prognostic implications**
- **The majority of patients have an atopic tendency or a family history of atopy. There is a particularly strong association between atopic dermatitis and atopic keratoconjunctivitis**
- **The mainstays of treatment for the majority of allergic eye disease symptoms are topical eye drops, including antihistamines, mast cell stabilizers and anti-inflammatory agents**
- **Topical steroid preparations are the most effective therapy for moderate to severe forms of allergic eye disease but their use should be limited to these cases and the eye monitored carefully for steroid related side effects such as cataracts and glaucoma**
- **Topical calcineurin inhibitors may be of benefit as steroid sparing agents or in the treatment of allergic eye disease where the disease is failing to respond to steroid treatment**

References

1. Aguilar AJ (2000) Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. Acta Ophthalmol Scand Suppl 78:52–55
2. Akpek EK, Dart JK, Watson S, Christen W, Dursun D, Yoo S, O'Brien TP, Schein OD, Gottsch JD (2004) A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. Ophthalmology 111(3):476–482
3. Allansmith MR, Korb DR, Greiner JV, Henriquez AS, Simon MA, Finnemore VM (1977) Giant papillary conjunctivitis in contact lens wearers. Am J Ophthalmol 83:697–708
4. Artal M, Luna J, Discepola M (2000) A forced choice comfort study of olopatadine hydrochloride 0.1% versus ketotifen fumarate 0.05%. Acta Ophthalmol Scand 78:64–65
5. Ashrafzadeh A, Raizman MB (2003) New modalities in the treatment of ocular allergy. Int Ophthalmol Clin 43(1):105–110
6. Bawazeer AM, Hodge WG, Lorimer B (2000) Atopy and keratoconus: a multivariate analysis. Br J Ophthalmol 129:667–668
7. Bielory L (2000) Allergic and immunologic disorders of the eye, part II: ocular allergy. J Allergy Clin Immunol 106:1019–1032
8. Bielory L (2002) Ocular allergy guidelines: a practical treatment algorithm. Drugs 62(11):1611–1634
9. Bielory L, Kempuraj D, Theoharides T (2002) Topical immunopharmacology of ocular allergies. Curr Opin Allergy Clin Immunol 2:435–445
10. Bonini S, Bonini S (1998) Pathogenesis of allergic conjunctivitis. In: Denburg JA (ed) Allergy, allergic diseases: the new mechanisms and therapeutics. Humana Press, Totowa, NJ
11. Bonini S, Bonini S, Lambaste A, March S, Pasqualetti P, Zuccaro O, Rama P, Magrini L, Juhas T, Bucci MG (2000) Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term follow up. Ophthalmology 107:1157–1163
12. Bonini S, Coassin M, Aronni S, Lambiase A (2004) Vernal keratoconjunctivitis. Eye 18:345–351
13. Butrus S, Greiner JV, Discepola M, Finegold I (2000) Comparison of the clinical efficacy and comfort of olopatadine hydrochloride 0.1% ophthalmic solution and nedocromil sodium 2% ophthalmic solution in the human conjunctival allergen challenge model. Clin Ther 22:1462–1472
14. Cook EB, Stahl JL, Barney NP, Graziano FM (2000) Olopatadine inhibits TNFalpha release from human conjunctival mast cell. Ann Allergy Asthma Immunol 84:504–508

15. Donshik PC, Pearlman D, Pinnas J, Raizman MB, Tauber J, Tinkelman D, Walters TR (2000) Efficacy and safety of ketorolac tromethamine 0.5% and levocabastine 0.05%: a multicentre comparison in patients with seasonal allergic conjunctivitis. Adv Ther 17(2):94–102
16. Easty DL, Entwistle C, Fund A, Witcher J (1975) Herpes simplex keratitis and keratoconus in the atopic patient: a clinical and immunological study. Transcripts Ophthalmol Soc UK 95:267–276
17. Fahy GT, Easty DL, Collum LM, Benedict-Smith A, Hillery M, Parsons DG (1992) Randomized double-masked trial of lodoxamide and sodium cromoglycate in allergic eye disease. A multicentre study. Eur J Ophthalmol 2(3):144–149
18. Foster CS, Calonge MD (1990) Atopic keratoconjunctivitis. Ophthalmology 97:992–1000
19. Fukagawa K, Nakajima T, Saito H, Tsubota K, Shimmura S, Natori M, Hirai K (2000) IL-4 induces eotaxin production in corneal keratocytes but not in epithelial cells. Int Archiv Allergy Immunol 121:144–150
20. Heinz C, Fanihagh F, Steuhl KP (2003) Squamous cell carcinoma of the conjunctiva in patients with atopic eczema. Cornea 22:135–137
21. Hingorani M, Moodaley L, Calder VL, Buckley RJ, Lightman S (1998) A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. Ophthalmology 105(9):1715–1720
22. Hogan MJ (1953) Atopic keratoconjunctivitis. Am J Ophthalmol 36:937–947
23. John T (2000) Contact lens-induced allergic reactions. In: Abelson MB (ed) Allergic diseases of the eye. WB Saunders, Philadelphia
24. Kallen C, Reinhard T, Schilgen G, Cartsburg O, Bocking A, Auw-Hadrich C, Sundmacher R (2003) Atopic keratoconjunctivitis: probably a risk factor for the development of conjunctival carcinoma. Ophthalmologie 100:808–814
25. Keane-Myers AM, Miyazaki D, Liu G, Dekaris I, Ono SJ, Dana MR (1999) Prevention of allergic eye disease by treatment with IL-1 receptor antagonist. Invest Ophthalmol Vis Sci 40(12):3041–3046
26. Korb DR, Allansmith MR, Greiner JV, Henriquez AS, Herman JP, Richmond PP, Finnemore VM (1981) Biomicroscopy of papillae associated with hard contact lens wearing. Ophthalmology 88: 1132–1136
27. Korb DR, Allansmith MR, Greiner JV, Henriquez AS, Richmond PP, Finnemore VM (1980) Prevalence of conjunctival changes in wearers of hard contact lenses. Am J Ophthalmol 90:336–341
28. Larkin DFP (1999) Immunological, neoplastic and degenerative diseases of the conjunctiva. In: Easty D, Sparrow J (eds) The Oxford textbook of ophthalmology. Oxford University Press, Oxford
29. Leonardi A, Busato F, Fregona I, Plebani M, Secchi AG (2000) Anti-inflammatory and antiallergic effects of ketorolac tromethamine in the conjunctival provocation model. Br J Ophthalmol 84(11): 1228–1132
30. Leonardi A, Secchi AG (2003) Vernal keratoconjunctivitis. Int Ophthalmol Clin 43:41–58
31. McGill J (2000) Conjunctival cytokines in ocular allergy. Clin Exp Allergy 30:1355–1357
32. McGill JI, Holgate ST, Church MK, Anderson DF, Bacon A (1998) Allergic disease mechanisms. Br J Ophthalmol 82:1203–1214
33. Messmer EM, May CA, Stefani FH, Welge-Luessen U, Kampik A (2002) Toxic eosinophil granule protein deposition in corneal ulceration and scars associated with atopic keratoconjunctivitis. Am J Ophthalmol 134:816–821
34. Metz DM, Bonini S, Lightman S (1993) mRNA expression for interleukin-2 interleukin-5 in vernal keratoconjunctivitis. Invest Ophthalmol Vis Sci 34:772
35. Metz DP, Bacon AS, Holgate ST, Lightman S (1996) Phenotypic characterization of T-cells infiltrating the conjunctiva in chronic allergic eye disease. J Allergy Clin Immunol 98:686–696
36. Miyazaki D, Liu G, Clark L, Ono SJ (2000) Prevention of acute allergic conjunctivitis and late phase inflammation with immunostimulatory DNA sequences. Invest Ophthalmol Vis Sci 41(12):3850–3855
37. Miyazaki D, Nakamura T, Komatsu N, Nawata N, Ikeda Y, Inoue Y, Higashi H, Ono SJ (2004) Roles of chemokines in ocular allergy and possible therapeutic strategies. Cornea 23(Suppl 1):S48–54
38. Miyazaki D, Nakamura T, Toda M, Cheung-Chau KW, Richardson R, Ono SJ (2005) Macrophage inflammatory protein-1alpha as a costimulatory signal for mast cell mediated immediate hypersensitivity reactions. J Clin Invest 115:434–442
39. Montan PG, Ekstrom K, Hedlin G, van Hage-Hamsten M, Hjern A, Herrmann B (1999) Vernal keratoconjunctivitis in a Stockholm ophthalmic centre: epidemiological, functional and immunological investigations. Acta Ophthalmol Scand 77:559–563
40. Nishimura A, Campbell-Meltzer RS, Chute K, Orrell J, Ono SJ (2001) Genetics of allergic disease: evidence for organ-specific susceptibility genes. Int Archiv Allergy Immunol 124:197–200

41. Ono SJ, Abelson MB (2005) Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 115: 118–122
42. Raizman MB, Rothman JS, Maroun F, Rand WM (2000) Effect of rubbing on signs and symptoms of allergic conjunctivitis in cat-sensitive individuals. Ophthalmology 107(12):2158–2161
43. Santos CI, Huang AK, Abelson MB, Foster CS, Friedlaender M, McCulley JP (1994) Efficacy of lodoxamide 0.1% ophthalmic solution in resolving corneal epitheliopathy associated with vernal keratoconjunctivitis. Am J Ophthalmol 117(4): 488–497
44. Sharif NA, Xu SX, Miller ST, Gamache DA, Yanni JM (1996) Characterization of the ocular antiallergic and antihistaminic effects of olopatadine (AL-4943A), a novel drug for treating ocular allergic diseases. J Pharmacol Exp Ther 278(3): 1252–1261
45. Sitenga GL, Ing EB, Van Dellen RG, Younge BR, Leavitt JA (1996) Asthma caused by topical application of ketorolac. Ophthalmology 103(6):890–892
46. Solomon A, Pe'er J, Levi-Schaffer F (2001) Advances in ocular allergy: basic mechanisms, clinical patterns and new therapies. Curr Opin Allergy Clin Immunol 1:477–482
47. Solomon A, Puxeddu I, Levi-Schaffer F (2003) Fibrosis in ocular allergic inflammation: recent concepts in pathogenesis of ocular allergy. Curr Opin Allergy Clin Immunol 3:389–393
48. Stahl JL, Barney NP (2004) Ocular allergic disease. Curr Opin Allergy Clin Immunol 4:455–459
49. Tabbara KF (2003) Immunopathogenesis of chronic allergic conjunctivitis. Int Ophthalmol Clin 43(1):1–7
50. Takano Y, Fukagawa K, Dora M, Santo-Kato N, Tsubota K, Fujishima H (2004) Inflammatory cells in brush cytology samples correlate with the severity of corneal lesions in atopic keratoconjunctivitis. Br J Ophthalmol 88:1504–1505
51. Trocme SD, Karan KS (2002) Spectrum of ocular allergy. Curr Opin Allergy Clin Immunol 2:423–427
52. Tuft SJ, Dart JK, Kemeny M (1989) Limbal vernal keratoconjunctivitis: clinical characteristics and IgE expression compared with palpebral vernal. Eye 3:420–427
53. Tuft SJ, Kemeny DM, Dart JK, Buckley RJ (1991) Clinical features of atopic keratoconjunctivitis. Ophthalmology 98(2):150–158
54. Tuft SJ, Ramakrishnan M, Seal DV, Kemeny DM, Buckley RJ (1992) Role of *Staphylococcus aureus* in chronic allergic conjunctivitis. Ophthalmology 99:180–184
55. Wakai K, Okamoto K, Tamakoshi A, Lin Y, Nakayama T, Ohno Y (2001) Seasonal allergic rhinoconjunctivitis and fatty acid intake: a cross-sectional study in Japan. Ann Epidemiol 11(1): 59–64
56. Yokoi K, Yokoi N, Kinoshita S (1998) Impairment of ocular surface epithelium barrier function in patients with atopic dermatitis. Br J Ophthalmol 82:797–800
57. Yoneda K, Okamoto H, Wada Y, Morita K, Takahashi M, Ogura Y, Imamura S (1995) Atopic retinal detachment: report of 4 cases and a review of the literature. Br J Dermatol 133(4):586–591