

POSITION PAPER

Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface

A. Leonardi¹, E. Bogacka², J. L. Fauquert³, M. L. Kowalski⁴, A. Groblewska⁵,
M. Jedrzejczak-Czechowicz⁴, S. Doan⁶, F. Marmouz⁷, P. Demoly⁸ & L. Delgado⁹

¹Department of Neuroscience, Ophthalmology Unit, University of Padua, Padua, Italy; ²Department of Internal Medicine, Allergy and Geriatrics, Medical Academy of Wrocław, Wrocław, Poland; ³Unité d'Allergologie de l'enfant, CHU Estaing, Clermont-Ferrand, France; ⁴Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Łódź, Poland; ⁵Department of Ophthalmology, Polish Mother's Memorial Hospital, Łódź, Poland; ⁶Hopital Bichat and Fondation A. de Rothschild, Paris, France; ⁷Pole sanitaire du Vexin, Pontoise, France; ⁸Inserm U454 – IFR3, hôpital Arnaud-de-Villeneuve, Montpellier, France; ⁹Faculty of Medicine, Department of Immunology, University of Porto, Porto, Portugal

To cite this article: Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, Doan S, Marmouz F, Demoly P, Delgado L. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012; DOI: 10.1111/all.12009.

Keywords

allergy; diagnosis; keratoconjunctivitis;
ocular; treatment.

Correspondence

Andrea Leonardi, Department of
Neuroscience, Ophthalmology Unit,
University of Padua,
Via Giustiniani 2, Padua 35128, Italy.
Tel.: +390498212979
Fax: +390498755168
E-mail: andrea.leonardi@unipd.it

Task Force Report from the EAACI Ocular
Allergy Interest Group on Diagnosis and
Management of Ocular Allergy.

Accepted for publication 20 July 2012

DOI:10.1111/all.12009

Edited by: Thomas Bieber

Abstract

Ocular allergy includes several clinically different conditions that can be considered as hypersensitivity disorders of the ocular surface. The classification of these conditions is complex, and their epidemiology has not been adequately studied because of the lack of unequivocal nomenclature. Ocular allergy symptoms are often, but not always, associated with other allergic manifestations, mostly rhinitis. However, specific ocular allergic diseases need to be recognized and managed by a team that includes both an ophthalmologist and an allergist. The diagnosis of ocular allergy is usually based on clinical history and signs and symptoms, with the support of *in vivo* and *in vitro* tests when the identification of the specific allergic sensitization is required for patient management. The aims of this Task Force Report are (i) to unify the nomenclature and classification of ocular allergy, by combining the ophthalmology and allergy Allergic Rhinitis and its Impact on Asthma criteria; (ii) to describe current methods of diagnosis; (iii) to summarize the therapeutic options for the management of ocular allergic inflammation.

Ocular allergy is a localized allergic condition that is observed as the only or dominant presentation of an allergic sensitization, or is associated with rhinitis. It is not a single clinical entity, but includes several conditions with different pathogenesis, hypersensitivity mechanisms, diagnostic criteria, and management. Ocular allergies are encountered daily in the physician's office. Approximately 15–20% of the world population is affected by some form of allergic disease; ocular symptoms are estimated to be present in 40–60% of allergic patients (1) and contribute significantly to poor quality of life (2–4). Most of the available prevalence data encompass both ocular and nasal symptoms, making it impossible to separate ocular allergy from allergic rhinitis. Moreover, the frequently confusing nomenclature makes estimations of prevalence difficult.

The purpose of this position paper is to unify the nomenclature and classification of ocular allergies, in order to facilitate the exchange of information and knowledge on diagnosis and management between allergists and ophthalmologists. The existing evidence for treatment options was evaluated using the SIGN criteria (5).

Classification and nomenclature

The ocular allergy nomenclature is based either on clinical signs and symptoms (Table 1) or on pathophysiology, according to the different hypersensitivity mechanisms introduced by Gell and Coombs. In 2001, the European Academy of Allergy and Clinical Immunology (EAACI)

introduced a revised nomenclature that proposed a distinction between *allergic* and *nonallergic* hypersensitivity reactions: *allergic* diseases were further divided into IgE- and non-IgE-mediated hypersensitivities (6). This was validated by the Nomenclature Review Committee of the World Allergy Organization (WAO) (7), who proposed that the nomenclature could be used independently of the target organ or patient age group.

Here, we propose a new classification for ocular allergic disorders (Fig. 1). If allergic ocular hypersensitivity is suspected, identification of the immunological mechanism(s) is justified and potential immunomodulatory treatment can be considered. In contrast, in nonallergic ocular hypersensitivities, different therapeutic strategies should be considered.

A classification based on both pathophysiology and the evolution of the symptoms has been proposed (8). According to the Allergic Rhinitis and its Impact on Asthma (ARIA) document (9), symptoms should be considered as intermittent or persistent, and mild, moderate, or severe according to their evolution and severity. To adapt this classification to ocular hypersensitivity disorders, some points must be considered: these are outlined in Tables 2 and 3.

Clinical entities

Seasonal allergic conjunctivitis (SAC) is a typical IgE-mediated allergic reaction, usually associated with rhinitis. It is more prevalent from the spring to fall seasons when pollen levels are high. The hallmark symptom is intermittent itching; however, tearing, conjunctival redness, eyelid swelling, and small papillary hypertrophy of tarsal conjunctiva are common but nonspecific signs. Signs and symptoms arise and subside depending on the patient's exposure to the offending

allergen(s). An accurate medical history followed by allergy testing may identify the specific sensitization (see Investigation of ocular allergy).

Perennial allergic conjunctivitis (PAC) is an IgE-mediated reaction to allergens that are present all year-round, such as dust mites, animal dander, and molds, or due to multiple sensitizations. It is characterized by the same signs and symptoms as SAC (Fig. 2A); however, PAC is a chronic condition, with persistent, frequently mild symptoms, enhanced by higher or longer exposure to allergens and exacerbated by nonspecific irritating factors. Neither SAC nor PAC has corneal involvement; however, they affect the patient's quality of life and have a significant socioeconomic impact (2–4, 10).

Vernal keratoconjunctivitis (VKC) is a persistent and severe form of ocular allergy that affects children and young adults, usually in warm climates. Vernal keratoconjunctivitis typically appears in boys between the age of 4–12 years (sex ratio, 3/1) and disappears after puberty. The IgE-mediated mechanism found in approximately 50% of patients does not completely explain the severity and the clinical course of this disease, which is related to a T-cell-mediated responses, massive eosinophil infiltration and activation, and nonspecific hyper-reactivity. Intense itching, tearing, and photophobia are the typical symptoms of VKC. Disease exacerbation can be triggered either by allergen re-exposure or, more frequently, by nonspecific stimuli such as sunlight, wind, and dust. The *tarsal* form of VKC is characterized by irregularly sized hypertrophic papillae, leading to a cobblestone appearance of the upper tarsal plate (Fig. 2B). Asymmetric tarsal involvement is not unusual. The *limbal* form is characterized by transient, multiple limbal, or conjunctival gelatinous yellow-gray infiltrates superposed with white points or deposits, known as Horner–Trantas dots (degenerating eosinophils and

Table 1 Clinical features of major ocular allergy syndromes, including the underlying hypersensitivity mechanism and ophthalmological presentation

	SAC	PAC	VKC	AKC	GPC	CBC
Presentation	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Persistent	Chronic ± intermittent exacerbations
Allergic Mechanism	IgE-mediated	IgE-mediated	IgE- and non-IgE-mediated	IgE- and non-IgE-mediated	Nonallergic	Non-IgE-mediated
Background	Atopic	Atopic	Childhood ± atopic	Adult atopic	Atopic or nonatopic	Nonatopic
Eyelids	Edema	±Edema	Edema Pseudoptosis	Eczema + meibomitis blepharitis	–	Erythema, eczema
Conjunctiva	Follicles and/or papillae	Follicles and/or papillae	Giant papillae	Papillae ± fibrosis	Giant papillae	±Hyperemia Follicles
Limbus	–	–	±Thickened +Trantas dots	±Thickened ±Trantas dots	Hyperemia	–
Cornea	–	–	SPK ±Ulcer ±Vernal plaque	SPK Ulcer, Plaque, Opacities, neovascularization	Rare	–

SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; CBC, contact blepharoconjunctivitis; SPK, superficial punctate keratitis.

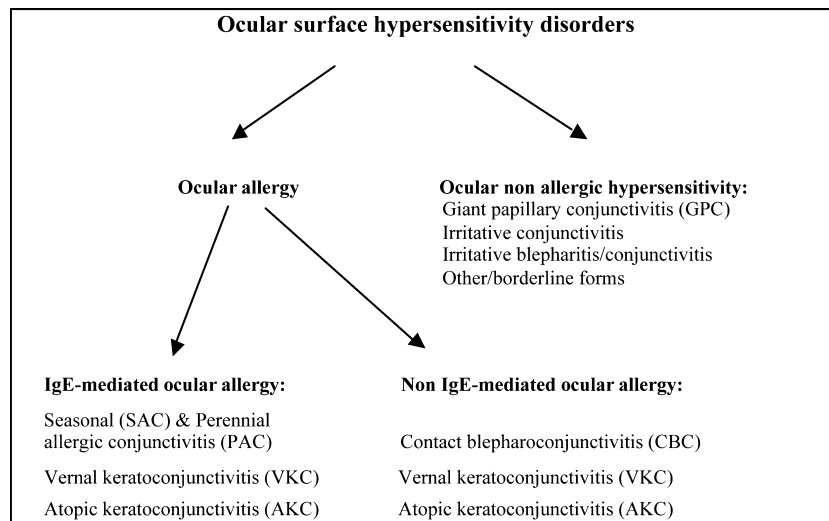


Figure 1 New classification based on pathophysiology and hypersensitivity nomenclature proposed by the Task Force. Note that

both IgE- and T-cell-dependent mechanisms have been shown in vernal and atopic keratoconjunctivitis.

Table 2 Ocular allergy: arguments for and against using a common symptom and severity classification based on allergic rhinitis and its impact on asthma

Argument for	Argument against
Frequent clinical association eye/nose	The eye can be the only target organ
Shared pathophysiological mechanisms with allergic rhinitis	Etiological factors are not exclusively allergic
Same environmental exposure and triggers in common	Local factors and nonspecific stimuli can trigger ocular surface symptoms independently of sensitization
Terms 'seasonal and perennial' are not appropriate to variable climate seasons	Contact blepharoconjunctivitis is not associated with nasal involvement
Some common therapeutic approaches	Specific treatment if initial ophthalmic complications [†]
Patient's point of view*	Some treatments (e.g., topical immunosuppressors) need ophthalmologic monitoring
	Lack of validated studies in ocular allergy

*A patient also with rhinitis may have difficulty in understanding different nomenclatures for the disease from which they are suffering.

[†]Ophthalmologic support can be justified before any other measure in the case of an inaugural complication (e.g., corneal ulcers).

epithelial cell debris) and papillae at the limbus, which may appear thickened and opacified for 360° (Fig. 2C,D). Punctate keratitis, epithelial macroerosions, ulcers (Fig. 2E), and plaques (Fig. 2F) are signs of corneal involvement and resolve with different levels of scarring. The clinical presentations of VKC differ between western (tarsal forms) and sub-tropical countries (limbal form, also named endemic tropical limboconjunctivitis) (11).

Atopic keratoconjunctivitis (AKC) is a persistent inflammatory, bilateral condition involving the eyelids, the conjunctiva, and possibly the cornea and can be defined as the ocular manifestation of atopic dermatitis. IgE-, Th2-, and Th1-mediated mechanisms are involved in the pathogenesis. Typical AKC manifestations may occur in patients without definite skin involvement. The hallmark sign is eczematous lesion of the eyelid, which tends to thicken, indurate, and fissure (Fig. 2G). Atopic keratoconjunctivitis may be associated with *Staphylococcus aureus* colonization of the eyelid and meibomian gland dysfunction. The conjunctival redness and

chemosis affect predominantly the inferior fornix and palpebral conjunctiva. Similar to VKC, the limbus and the cornea can be involved. Generally, AKC emerges in young adults and continues through the fifth decade of life, with a peak incidence between the age of 30–50. Complications can include conjunctival fibrosis, herpes simplex keratitis, keratoconus, retinal detachment, or cataracts, leading to sustained deterioration of vision. An accurate medical history followed by allergy testing may identify sensitization to specific allergens (see Investigation of ocular allergy).

Giant papillary conjunctivitis (GPC) is a nonallergic hypersensitivity inflammation of the ocular surface, most frequently to contact lenses, ocular prostheses, postoperative sutures, and scleral buckles. The early stages of GPC may be asymptomatic, but initial signs can be observed by slit lamp examination (Fig. 2H). In the case of contact lenses, progression to foreign body sensation, itching, blurred vision, increased mucus production, and increasing intolerance may necessitate discontinuation.

Table 3 Grading of symptoms and severity of hypersensitivity disorders at the ocular surface based on allergic rhinitis and its impact on asthma criteria

A. Persistence of symptoms	
'Intermittent'	means that the symptoms (itching and redness) are present:
	Less than 4 days a week
	Or for less than 4 weeks
'Persistent'	means that the symptoms (itching and redness) are present:
	More than 4 days a week
	And for more than 4 weeks
B. Severity of symptoms	
'Mild'	means that none of the following items are present:
	Vision disturbance
	Impairment of daily activities, leisure, and/or sport
	Impairment of school or work
	Troublesome symptoms
'Moderate'	means that one of the following items are present:
	Vision disturbance
	Impairment of daily activities, leisure, and/or sport
	Impairment of school or work
	Troublesome symptoms
'Severe'	means that two or more of the following items are present:
	Vision disturbance
	Impairment of daily activities, leisure, and/or sport
	Impairment of school or work
	Troublesome symptoms

Contact blepharoconjunctivitis (CBC) is an allergic/irritant reaction to different substances applied to the eyelid skin or the conjunctival SAC. The most prominent symptoms are itching and burning of the eyelid. Contact blepharoconjunctivitis is characterized by edema, eyelid skin redness, eczema or lichenification, conjunctival redness, and papillae (Fig. 2I). Eczema on the eyelid skin and absence of conjunctival hyperemia indicate that the irritant has been in contact only with the eyelid.

Special clinical entities

Acute allergic conjunctivitis is a severe, immediate hypersensitivity reaction, lasting from one to three days, and characterized by intense conjunctival chemosis, eyelid redness and edema, eye watering, and itching. It can be mono- or bilateral and caused by IgE-mediated, non-IgE-mediated, or toxic reactions. It can be also related to food- or drug-induced systemic allergic reaction (12).

Occupational allergic conjunctivitis is an IgE-dependent allergic reaction to airborne substances in the workplace (13).

Drug-induced conjunctivitis is a persistent or chronic conjunctivitis, also referred to as conjunctivitis *medicamentosa*. A toxic reaction may occur following instillation of eye drops, such as topical antiglaucoma agents, mydriatics, or alpha-adrenergic agonists commonly used as decongestants in

over-the-counter anti-allergy eye drops (14). Topical antibiotics, eye drops containing herbal extracts, and preservatives, such as benzalkonium chloride, thimerosal, parabens, and ethylenediaminetetraacetic acid (EDTA), may cause either a toxic reaction or a cell-mediated hypersensitivity response. The condition is characterized by an intense and persistent follicular reaction, associated with mild to intense hyperemia. The lacrimal puncta may be swollen or occluded by a cellular infiltrate with a consequent epiphora. The cornea is often involved as a diffuse punctate keratitis. Eyelid skin may be involved with erythema, swelling, and excoriation.

Irritant conjunctivitis, also known as toxic or mechanical conjunctivitis, is frequently confused with allergy. It is the result of destruction of junctures between epithelial cells, and epithelial cell toxicity following single or repeated exposure to chemical substances. A careful medical history and examination can exclude an allergic etiology. Clinical features are similar to drug-induced conjunctivitis.

Epidemiology

There are insufficient data to objectively evaluate the incidence of ocular allergies. To date, only the epidemiology of allergic rhinoconjunctivitis (ARC) has been well studied. According to the ISAAC study (International Study Asthma and Allergies in Childhood), ARC affects 1.4–39.7% of children and adolescents. The incidence and prevalence of ARC increase from infancy and peaks in childhood and adolescence (15). In 80% of cases, symptoms develop before the age of 20 years. According to ARIA, seasonal ARC affects 3–42% of the population (depending on different climatic conditions and age groups), with persistent ARC affecting 1–18% (9). In a study of 458 children affected by rhinitis (316), asthma (324), and eczema (149), the prevalence of allergic conjunctivitis was 42%, 24%, and 30%, respectively (16). 137 (30%) had allergic conjunctivitis, of whom 97% also had allergic rhinitis, 56% asthma, and 33% eczema.

In the NHANES III survey with a sample size of 20 010, 40% of the population reported at least one ocular allergy symptom (17). Ocular allergy was twice as common as allergic rhinitis (18). The most common form was SAC. On the other hand, the prevalence of PAC seems to be underestimated by both ophthalmologists and allergists (19). In a study of 19 325 subjects, PAC was associated with coexisting mite allergy in 46% of patients with allergic rhinitis (20).

Vernal keratoconjunctivitis is a rare disease in western countries. The estimated prevalence in Europe is 3.2/10 000, whereas it is almost endemic in subtropical countries (21). It represents 3–46% of ocular allergies (10). Warm climates and sun exposure probably explain the characteristic north–south gradient of prevalence.

Atopic keratoconjunctivitis is a rare disease, and its prevalence is not clear. Whereas ocular involvement is seen in 25–40% of patients with atopic dermatitis, AKC is probably much less frequent. The reported rates range from 1 to 40% of ocular allergies, which probably reflects the lack of a clear definition of this disease (10, 17).

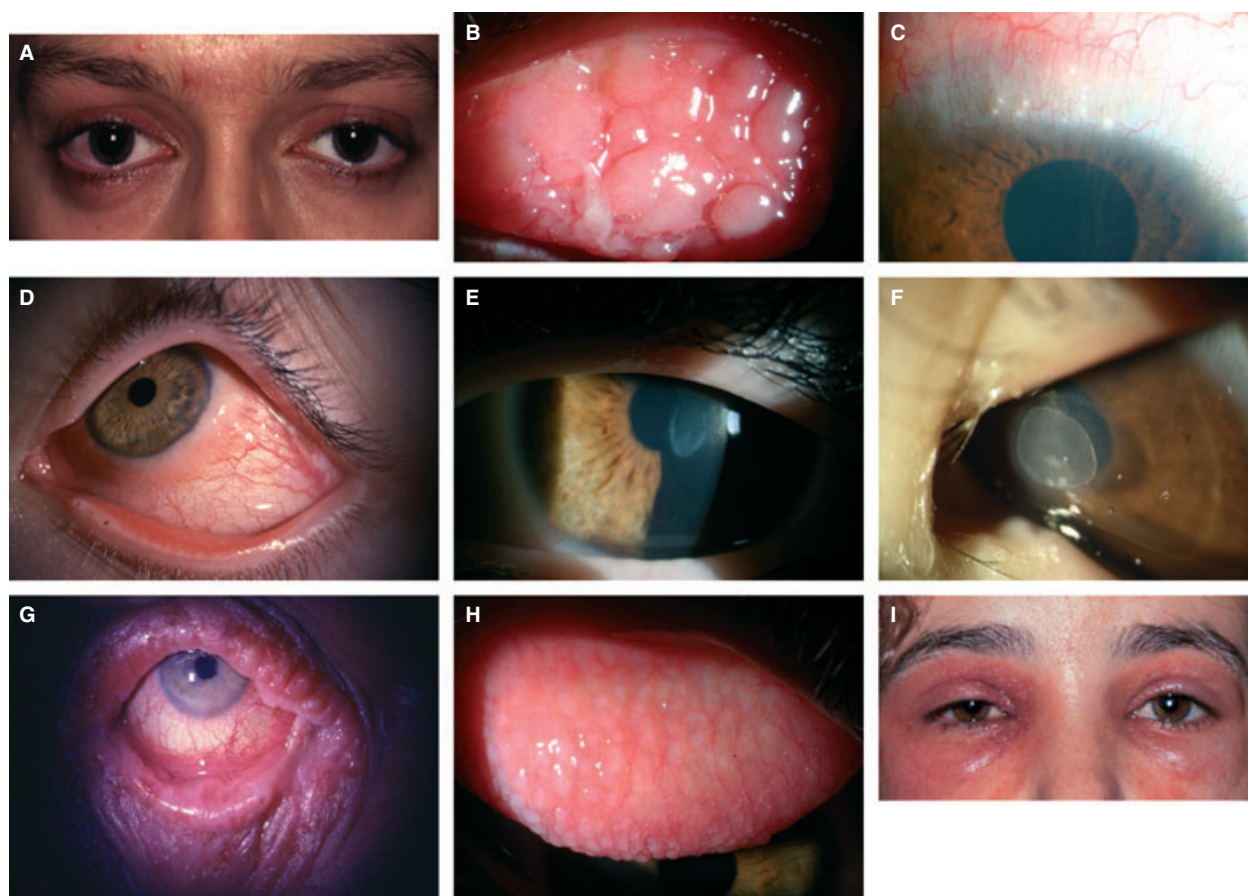


Figure 2 Clinical features of the major ocular allergy syndromes: (A) mild conjunctival redness and lid edema in perennial allergic conjunctivitis; (B) tarsal form of vernal keratoconjunctivitis (VKC) with giant papillae; (C) Trantas dots in limbal VKC; (D) limbal form

of VKC; (E) central corneal ulcer in VKC; (F) corneal plaque in VKC; (G) skin lesion in atopic keratoconjunctivitis; (H) tarsal papilla in contact lens associated giant papillary conjunctivitis; (I) skin lesion in contact blepharoconjunctivitis.

Pathophysiology

IgE-mediated ocular allergy: seasonal allergic conjunctivitis and perennial allergic conjunctivitis

Specific IgE-mediated conjunctival mast cell activation induces the immediate conjunctival allergic response. This lasts 20–30 min, as demonstrated by specific conjunctival allergen challenge (CAC) (22), and is characterized by increased levels of histamine, tryptase, prostaglandins, and leukotrienes in the tears (23). Conjunctival mast cells are 100% tryptase+ and chymase+ and express IL-4, which plays a key role in allergy, promoting T-cell growth, Th2 cell differentiation, and IgE production (24). The late-phase conjunctival allergic response, characterized by infiltration of inflammatory cells, occurs few hours after the first mast cell activation and expression of adhesion molecules (25). Activated mast cells also release several cytokines that stimulate epithelial cells and fibroblasts to produce pro-inflammatory cytokines and chemokines (26), leading to persistent conjunctival inflammation.

Seasonal allergic conjunctivitis patients have a predominant Th2 phenotype (27), but also have a reduced expression of

epithelial cell adhesion proteins and cytoskeletal elements, which suggests a reduced ability of the epithelium to protect itself against penetration of the allergen (28).

IgE- and/or non-IgE-mediated ocular allergy: vernal keratoconjunctivitis and atopic keratoconjunctivitis

Vernal keratoconjunctivitis is a persistent and severe form of ocular allergy, characterized by massive infiltration of T cells, macrophages, neutrophils, and especially eosinophils. It can be considered as a severe persistent late-phase reaction (29). It is unclear why the incidence varies with age and geographical region.

Increased numbers of CD4+ Th2 cells, increased expression of costimulatory molecules, and multiple cytokines and chemokines have been described in VKC. These act concomitantly to induce local production of IgE (30), in the pathogenesis of the corneal involvement and tissue remodeling (31–34). Direct activation of allergen-specific T cells by antigens or direct activation of dendritic cells may be alternative pathways for initiating the reaction without evidence of specific IgE sensitization (35). In fact, specific

IgE are identified in only 50% of patients (36), supporting the concept that non-IgE-mediated activation pathways are present. In addition, several enzymatic systems, metalloproteases, and their inhibitors may be activated, contributing to structural cell activation and tissue remodeling (37). Nonspecific hyper-reactivity is another typical aspect, which is, in part, due to the altered expression of neuroreceptors and neurotransmitters (38).

Atopic keratoconjunctivitis is the ocular manifestation of atopic dermatitis. Although 45% of patients do not have any specific sensitization, high serum IgE level and polysensitization are common findings in AKC (39). High levels of multiple cytokines and chemokines have been detected in tears, suggesting that both Th1 and Th2 responses may be activated (40, 41). Atopic keratoconjunctivitis is associated with qualitative and/or quantitative alterations of the mucous component of the tear film, causing mucus discharge, epithelial disease, dry eye signs and symptoms, and the lower stability of the tear film (42). It is also possible that mechanisms related to the activation of innate immunity receptors (Toll-like receptors) play an active role in the chronic inflammatory response (43).

Non-IgE-mediated ocular allergy: contact blepharoconjunctivitis

Contact blepharitis or blepharoconjunctivitis is related to a contact T-cell-mediated delayed hypersensitivity reaction to haptens (incomplete antigens), which become immunogenic only after they bind to tissue protein (14).

Ocular nonallergic hypersensitivity: giant papillary conjunctivitis

Giant papillary conjunctivitis is caused by two factors: a repeated mechanical stimulus and an abnormal conjunctival inflammatory response. Microtrauma of the conjunctiva can be caused by all types of contact lenses. Lens design, polymer constitution, wearing period, and fitting characteristics can influence the development of GPC. The mechanical irritation may stimulate the recruitment of dendritic cells, potentially enhancing antigen presentation and immune responsiveness (44).

Investigation of ocular allergy

Three types of diagnostic investigations are currently used when the initial clinical assessment (history, signs, and symptoms) is suggestive of an ocular allergic disease: (1) to highlight IgE-mediated hypersensitivity; (2) to highlight non-IgE-mediated hypersensitivity; and (3) specialized ocular investigations.

- 1 To highlight IgE-mediated hypersensitivity, skin prick tests (SPTs) should be performed systematically for pollens, mites, animal dander, and *alternaria* (6, 7). Other allergens (cockroach, molds, and latex) or food allergens should be tested, according to the suspected exposure and patient's medical history.

Serum-specific IgE measurements should be considered when SPTs are discordant with the medical history or contraindicated, or as an alternative to SPT to quantify specific IgE to naïve allergens and/or their purified components. The component-resolved diagnosis, based on the pure allergen molecules (microarray or recombinant allergen-specific IgE detection), may be helpful in the future for diagnosis in patients with multiple sensitizations (45).

Total serum IgE is no longer considered indispensable for diagnosis, because normal values do not exclude a diagnosis of allergy. Alternatively, the multiple allergen screening test may be useful (9).

Conjunctival provocation test (CPT)/Conjunctival allergen challenge (CAC) can determine or confirm which allergen (s) triggers the ocular symptoms (22). The patient should be asymptomatic and the eye should not be inflamed. Standardized allergens are available (46), and systemic side-effects (generalized itching, bronchospasm, anaphylaxis) are rare. Conjunctival provocation test is useful to evaluate the specific conjunctival response in patients with negative SPT or specific IgE, but a positive clinical history of ocular allergy (47), as well as to evaluate the effect of anti-allergic treatments and specific immunotherapy (22).

- 2 To highlight a non-IgE-mediated hypersensitivity, it is necessary to perform the patch test using the European battery (48) and suspected cosmetics. Other batteries are used according to the patient history. It must be emphasized that eyelid skin is quite different from that of the back, as regards the depth of the epithelial and dermal layers. If a patch test is negative, a repeated open application test (ROAT) or use application test can be performed (49). If topical drugs are suspected, the patch tests for ocular drugs and ingredients in eye drops and ROAT can be performed.
- 3 Specialized ocular investigations are necessary when traditional allergy test results are negative. Conjunctival cyto-diagnosis can assess conjunctival inflammation in the active phase and can be performed using different methods: *tear cytology*, *conjunctival scraping*, and *brush cytology* (a modification of the Cytobrush). *Impression cytology* is indicated to investigate epithelial cell pathology (50). The presence of eosinophils is highly indicative of allergic inflammation, while their absence does not exclude an allergic etiology.

Total tear IgE levels can increase in patients with allergic conjunctivitis, suggesting that tear IgE measurement can help to diagnose allergic conjunctivitis (51).

The tear-specific IgE assay is identical to that used for serum IgE measurement; however, there are no standardized reference parameters for the eye. A comparison between tear/serum IgE levels and a marker of serum transudation such as albumin may confirm local IgE production (52). However, the difficulty of tear collection, dilution, and the quantitative limits of the assay make CPT more appropriate to assess the specific conjunctival response.

The level of eosinophil cationic protein (ECP) in tears increases significantly in all forms of allergic conjunctivitis (53) and correlates with the severity of corneal involve-

ment during aggressive phases of VKC (53). In VKC, serum ECP is often the only abnormal laboratory parameter observed (36).

Inflammatory mediator measurements in tear fluid have been extensively used in ocular allergy either to find a 'disease marker', or to better understand the immune mechanisms involved and identify potential targets for therapeutic interventions. Multiplexed bead-based flow cytometry (31) and membrane or multiwell arrays (32) allow the simultaneous measurement of various mediators in a tear sample of few microliters, opening up further opportunities for diagnosis. Although several mediators can be detected, none is sufficiently standardized to be considered as a clear marker of ocular allergy and none of these techniques is standardized for the local use (50).

Tear film evaluation is performed by vital staining tests to demonstrate the epithelial integrity and the tear film function. Fluorescein stains epithelial defects, whereas rose bengal and lissamine green stain dead and damaged epithelial cells. Tear film stability can be measured by the break-up time. The Schirmer test is universally performed to diagnose the dry eye syndrome by evaluating tear film production.

In vivo confocal microscopy has been used to study several inflammatory and noninflammatory conditions, including severe ocular allergies (54, 55).

Table 4 Differential diagnosis of ocular allergy

Tear film dysfunction (dry eye)
Dry eye is the result of decreased tear production or increased tear evaporation.
Dry eye is more common in adults and is associated with systemic autoimmune disorders or senescence. However, tear film dysfunction can occur at any age.
Signs and symptoms include irritation, grittiness, burning, and foreign body sensation, but also itching.
Dry eye may be worsened by various medications including oral antihistamines, yet it can occur concomitantly to allergy.
Subacute and chronic infections
In bacterial conjunctivitis, the discharge is usually purulent with morning crusting around the eyelids.
Viral conjunctivitis is often seen in conjunction with a recent upper respiratory tract infection. Conjunctival hyperemia, chemosis, serous discharge, and corneal subepithelial opacities indicate a viral infection.
<i>Molluscum contagiosum</i> is a unilateral condition characterized by the typical lesions on the eyelid skin or margin.
<i>Chlamydial</i> conjunctivitis is characterized by a follicular persistent or chronic conjunctivitis.
Inflammatory conditions
Blepharitis is a common condition, characterized by eyelid margin hyperemia, ocular irritation, itching and discomfort caused by eyelid margin staphylococcal infection, meibomitis with or without seborrhea.
Frequently associated with blepharitis and dry eye are seborrhea, psoriasis, atopic dermatitis, and acne rosacea.
Ocular cicatricial pemphigoid, in the early stages, is a persistent conjunctivitis with subepithelial fibrosis at the internal canthus.

Differential diagnosis

Several clinical presentations may mimic the clinical features of hypersensitivity disorders of the ocular surface, including tear film dysfunction, subacute and chronic infections, and some autoimmune and inflammatory conditions (Table 4). These conditions should be considered by all physicians and must be confirmed by the ophthalmologist.

Milder forms of VKC may be confused with chronic perennial allergic conjunctivitis, phlyctenular keratoconjunctivitis, or trachoma (in endemic areas). Recurrent blepharitis with corneal involvement (ocular rosacea) can be confused with AKC or VKC. Mild cases of ocular cicatricial pemphigoid can mimic signs of AKC. Episcleritis and acute anterior uveitis are painful unilateral conditions that associate with autoimmune disorders.

Treatment for ocular allergy

The management of ocular allergy includes allergen avoidance, pharmacological treatment, immunotherapy, and patient education. The recommendations for allergen avoidance reported in the ARIA document should be followed (9), with the addition of wearing sunglasses to reduce direct ocular exposure to the airborne allergen. Cold compresses provide relief from symptoms (especially itching), and the use of lubricants (artificial tears) may improve the function of the ocular surface barrier. It is worth noting that most SAC and PAC patients treat themselves symptomatically or are treated by pharmacists or general practitioners (4).

Anti-allergic medication

Currently available topical drugs belong to several different pharmacological classes: antihistamines; mast cell stabilizers; mast cell stabilizers with antihistamine action, called 'dual-acting' agents; vasoconstrictors; nonsteroidal anti-inflammatory agents; corticosteroids; and calcineurin inhibitors. To minimize possible toxic effects of preservative compounds on the ocular surface, single-dose preservative-free eye drops should be used whenever possible in chronic forms of ocular allergy.

Topical antihistamines are competitive H1 receptor antagonists of varying specificity, potency, and duration of action. The first-generation H1 antagonists, pheniramine and antazoline, have a long safety record, but are known for their burning sensation upon instillation, their rapid onset but also rapid disappearance of effects, and their limited potency (56) (grade D). They are still available in association with vasoconstrictors in over-the-counter products. The second-generation H1 antagonists levocabastine and emedastine have a longer duration of action (4–6 h) and are better tolerated than their predecessors (57). Both drugs are effective and well tolerated also in pediatric patients (58) (grade C). They can be used in combination with mast cell stabilizers as maintenance treatment throughout the allergy season.

Oral antihistamines have been proven effective in relieving nasal and conjunctival symptoms (9, 56) (grade C). Accord-

ing to ARIA, second-generation antihistamines have the same efficacy than their predecessors, with a low-sedating profile and lack of anticholinergic activity (9) (grade C). When symptoms are primarily ocular, topical antihistamines should be preferred over systemic ones. Eye drops provide faster relief of ocular symptoms than systemic agents. Combination therapy with second-generation oral antihistamine and topical agents has been shown to be superior to oral treatment alone (56, 57) (grade C).

Mast cell stabilizers inhibit degranulation by interrupting the normal chain of intracellular signals that results from the activation of the IgE receptor (59). Used prophylactically, they inhibit the release of preformed inflammatory mediators and the arachidonic acid cascade and are effective in reducing signs and symptoms of ocular allergy. Several agents are available for topical use, including sodium cromoglycate 2% and 4%, nedocromil 2%, lodoxamide 0.1%, spaglumic acid 4%, and pemirolast 0.1% (not available in Europe) (60). They all require a preloading period (up to 2 weeks) and frequent installation (3–4 times/day), which sometimes results in poor compliance (56) (grade C).

Dual-action anti-allergic molecules azelastine, epinastine, ketotifen, and olopatadine (57) have the advantage of providing rapid relief from symptoms (owing to their antihistaminic effect) coupled with the long-term benefit of mast cell stabilization (57), making twice daily dosing possible (olopatadine 0.2% once a day is not available in Europe). Subtle distinctions between each of these drugs are likely to be reflected in differences in individual clinical outcomes. In patients with SAC, olopatadine, ketotifen, and epinastine were more effective than fluorometholone in preventing itching and hyperemia (61) (grade B).

Vasoconstrictors are alpha-adrenergic agonists approved for topical use in the relief of conjunctival redness, but have poor efficacy on other symptoms. Many of these products are marketed worldwide. Although they are well known and widely used, their short duration of action (2 h or less), significant stinging sensation, and tachyphylaxis limit their value when compared with the newer anti-allergic drugs (57) (grade D). Topical vasoconstrictors are not usually recommended because they are nonspecific and have no pharmacological action on the cascade of events underlying the allergic reaction.

The nonsteroidal anti-inflammatory drug (NSAID), ketorolac tromethamine 0.5%, is the only ophthalmic NSAID currently approved by the FDA for the relief of ocular itching in seasonal allergic conjunctivitis (62) (grade D). By blocking the synthesis of prostaglandins, in particular PGD_2 , NSAIDs partially inhibit the cascade of events that follows mast cell activation. Other NSAIDs, such as diclofenac, may also have some effect in controlling acute symptoms of seasonal allergic and vernal conjunctivitis (63) (grade D). These drugs should be used with caution in patients with a history of NSAID intolerance.

Topical Corticosteroids should be avoided in SAC and PAC; however, their use is, at times, inevitable in VKC and AKC when the cornea is involved. Corticosteroids do not directly stabilize immune cell membranes and do not inhibit histamine release. However, they may modulate the mast cell response by

inhibiting cytokine production and recruitment and activation of inflammatory cells. Thus, although they are not the first choice of therapy for ocular allergy, clinically, they are the most effective anti-inflammatory agents in active diseases. Topical fluorometholone, medrysone, loteprednol, rimexolone, and desonide eye drops, known as 'soft' corticosteroids, are the first choice in moderate inflammation (grade D). For severe allergic inflammation, prednisolone, dexamethasone, or betamethasone eye drops should be used, opting for the lowest dose and for the shortest duration of time. The therapeutic effects of the drugs, as well as the potential adverse effects (increased intraocular pressure, with a potential evolution toward glaucoma, cataract formation, bacterial, viral and fungal super-infections), must be monitored by an ophthalmologist, and the dose should be tapered slowly over several days. Hydrocortisone 1% cream on the eyelid skin is recommended for the treatment of severe acute eyelid eczema.

Even though nasal corticosteroids are not a first-line treatment for allergic conjunctivitis, in patients with rhinoconjunctivitis, nasal mometasone furoate (64) (grade A) and fluticasone furoate (65) (grade A) have been shown to improve the associated conjunctival symptoms. Although intranasal corticosteroids improve ocular symptoms, the involved mechanism(s), probably related to nose-ocular reflex reduction, is unknown. There are limited data on ocular safety; however, the literature supports their use over several months as there is no considerable increase in the risk of ocular hypertension or glaucoma (66).

Calcineurin inhibitors 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. Several reports have demonstrated the clinical benefit of topical cyclosporine (CsA) 1–2% eye drops in the treatment of severe VKC and AKC patients, ameliorating the signs and symptoms without significant adverse effects (grade D) (67, 68). A 0.05% ophthalmic emulsion has been approved by the FDA for the treatment of dry eye syndrome. Topical CsA 0.05% was not more effective than placebo as a steroid-sparing agent in steroid-dependent VKC patients (69) (grade B), but was effective in the long-term prevention of VKC relapses when compared with topical ketotifen (70) (grade A). In Japan, CsA 0.1% aqueous ophthalmic solution was shown to be effective and safe in the treatment of a large population of VKC and AKC patients (71) (grade C).

Tacrolimus and pimecrolimus dermatological creams are both licensed for the treatment of moderate-to-severe atopic eyelid diseases (72). Although patients may be at risk of local infectious complications, tacrolimus 0.1% (73) (grade C) and 0.03% ointments (74) and 1% pimecrolimus (75) (grade A) are effective in the treatment for severe ocular allergies.

Specific immunotherapy (SIT), using either subcutaneous or sublingual administration and different dosing schedules, has been reported to be effective in the treatment of patients affected by SAC and PAC. In the majority of studies, patients were diagnosed with allergic rhinoconjunctivitis; only a few studies were performed in patients with SAC

Table 5 Practical treatment for ocular allergy

A. How to treat IgE-mediated diseases: seasonal allergic conjunctivitis, perennial allergic conjunctivitis
Avoidance of clinically relevant allergens is the first step in the prevention of ocular allergy.
Topical antihistamines, mast cell stabilizers, or double-action drugs are the first choice of treatment.
Avoid topical corticosteroids, as they are rarely needed.
Topical vasoconstrictors should be used with caution.
Systemic antihistamines should be used in acute forms or when ocular symptoms are associated with other allergic comorbidities.
Consider specific immunotherapy when specific sensitization is the main cause of ocular allergy.
B. How to treat persistent/chronic forms (IgE- and non-IgE-mediated): vernal keratoconjunctivitis/atopic keratoconjunctivitis
Avoidance of specific and nonspecific triggers is the first step in the prevention of ocular allergy.
Use cold compresses, good eyelid hygiene, and lubricants.
Topical antihistamines, mast cell stabilizers, or double-action drugs are the first treatment choice, but may need to be used in combination. They should be used frequently during the day and during the whole season.
Topical corticosteroids should be used as short, pulsed therapy, when the cornea is involved.
Topical calcineurin inhibitors may be used in patients followed in specialized centers (off-label treatment in the EU).
Systemic anti-allergic drugs should be used when ocular symptoms are associated with other allergic comorbidities.
C. How to treat non-IgE-mediated diseases: contact blepharoconjunctivitis
Avoidance of irritants and/or sensitizing antigens.
Eyelid hygiene.
Emollients.
Topical corticosteroid ointments or dermatological creams should be used in the acute phases for the eyelid skin, with a preference for low-potency corticosteroids, such as hydrocortisone, desonide, and triamcinolone acetonide.
Oral antihistamines can be used to alleviate eyelid itching and inflammation.
Topical calcineurin inhibitors can be used in severe forms in patients followed in specialized centers (off-label treatment in the EU).

alone and one in VKC patients. Specific immunotherapy was effective in reducing total and individual ocular symptom scores (up to 40% reduction in itching) and use of eye drops (up to 63% reduction) in subjects with ARC or SAC, but not with PAC (76, 77) (grade A). Only in few studies was a

Table 6 Unmet needs in ocular allergy

The classification of ocular allergies is still unclear.
Well-conducted epidemiological studies are needed to determine the real prevalence and severity of ocular allergy.
Define the control and severity of ocular allergy and assess direct and indirect costs.
Define phenotypes/genotypes in relation to disease heterogeneity, immune responses, and inflammation, and their relevance to the severity and control of ocular allergy by medications or immunotherapy.
Define the role of allergens and panallergens in vernal keratoconjunctivitis and atopic keratoconjunctivitis.
Specific mediator and cellular mechanisms associated with particular types of ocular allergy must be identified and should lead to new diagnostic tools and novel therapies.
Novel treatments are needed to control symptoms in severe patients.

specific CPT performed before and after immunotherapy to assess patients' sensitivity to the allergen. In all cases, there was an increase in the allergen sensitivity threshold (78) (grade A).

Practical treatment for ocular allergy

See Table 5.

Conclusions and unmet needs

This position paper summarizes the current view regarding classification, pathophysiology diagnosis, and treatment for ocular allergy. It also aims to stimulate the interest, comprehension, and further investigations in this almost forgotten field, for both allergists and ophthalmologists. For example, it is still not clear why the eye can be the only target organ, or why some patients suffer from severe untreatable or chronic forms (Table 6). Ocular allergy suffers from a lack of resources, attracts low numbers of scientists, and requires more basic research. Pharmacological and immunological research has identified new possibilities to modifying the allergic immune response. This progress will continue, be applied to the eye, and eventually lead to complete control of moderate to severe forms of ocular allergy.

Conflict of interest

All authors have no commercial relationship or conflict of interest with the material presented.

References

1. Petricek I, Prost M, Popova A. The differential diagnosis of red eye: a survey of medical practitioners from Eastern Europe and the Middle East. *Ophthalmologica* 2006;**220**:229–237.
2. Smith AF, Pitt AD, Rodriguez AE, Alio JL, Marti N, Teus M et al. The economic and quality of life impact of seasonal allergic conjunctivitis in a Spanish setting. *Ophthalmic Epidemiol* 2005;**12**:233–242.
3. Pitt AD, Smith AF, Lindsell L, Voon LW, Rose PW, Bron AJ. Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. *Ophthalmic Epidemiol* 2004;**11**:17–33.

4. Palmares J, Delgado L, Cidade M, Quadra-do MJ, Filipe HP. Allergic conjunctivitis: a national cross-sectional study of clinical characteristics and quality of life. *Eur J Ophthalmol* 2010;**20**:257–264.
5. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;**323**:334–336.
6. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahela T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
7. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832–836.
8. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. *Curr Opin Allergy Clin Immunol* 2007;**7**:429–435.
9. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;**126**:466–476.
10. Uchio E, Kimura R, Migita H, Kozawa M, Kadosono K. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. *Graefes Arch Clin Exp Ophthalmol* 2008;**46**:291–296.
11. Diallo JS. Tropical endemic limboconjunctivitis. *Rev Int Trach Pathol Ocul Trop Subtrop* 1976;**53**:71–80.
12. Limsuwan T, Demoly P. Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). *Med Clin North Am* 2010;**94**:691–710.
13. Wittczak T, Pas-Wyroilak A, Palczynski C. Occupational allergic conjunctivitis. *Med Pr* 2007;**58**:125–130.
14. Baudouin C. Allergic reaction to topical eye-drops. *Curr Opin Allergy Clin Immunol* 2005;**5**:459–463.
15. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;**64**:123–148.
16. Gradman J, Wolthers OD. Allergic conjunctivitis in children with asthma, rhinitis and eczema in a secondary outpatient clinic. *Pediatr Allergy Immunol* 2006;**17**:524–526.
17. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988–1994. *J Allergy Clin Immunol* 2010;**126**:778–783.
18. Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;**2**(6 Pt 2):S805–S828.
19. Bielory L. Allergic and immunologic disorders of the eye. Part II: ocular allergy. *J Allergy Clin Immunol* 2000;**106**:1019–1032.
20. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallesstrini E et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005;**60**:882–887.
21. Bremond-Gignac D, Donadieu J, Leonardi A, Pouliquen P, Doan S, Chiambaretta F et al. Prevalence of vernal keratoconjunctivitis: a rare disease? *Br J Ophthalmol* 2008;**92**:1097–1102.
22. Abelson MB, Chambers WA, Smith LM. Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. *Arch Ophthalmol* 1990;**108**:84–88.
23. Leonardi A, Borghesan F, Faggian D, Depaoli M, Secchi AG, Plebani M. Tear and serum soluble leukocyte activation markers in conjunctival allergic diseases. *Am J Ophthalmol* 2000;**129**:151–158.
24. Anderson DF, Zhang S, Bradding P, McGill JJ, Holgate ST, Roche WR. The relative contribution of mast cell subsets to conjunctival TH2-like cytokines. *Invest Ophthalmol Vis Sci* 2001;**42**:995–1001.
25. Fukushima A, Yamaguchi T, Ishida W, Fukata K, Ueno H. Role of VLA-4 in the development of allergic conjunctivitis in mice. *Mol Vis* 2006;**12**:310–317.
26. Miyazaki D, Nakamura T, Toda M, Cheung-Chau KW, Richardson RM, Ono SJ. Macrophage inflammatory protein-1 α as a costimulatory signal for mast cell-mediated immediate hypersensitivity reactions. *J Clin Invest* 2005;**115**:434–442.
27. Cook EB, Stahl JL, Lowe L, Chen R, Morgan E, Wilson J et al. Simultaneous measurement of six cytokines in a single sample of human tears using microparticle-based flow cytometry: allergics vs. non-allergics. *J Immunol Methods* 2001;**254**:109–118.
28. Hughes JL, Lackie PM, Wilson SJ, Church MK, McGill JJ. Reduced structural proteins in the conjunctival epithelium in allergic eye disease. *Allergy* 2006;**61**:1268–1274.
29. Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res* 2002;**21**:319–339.
30. Abu El-Asrar AM, Fatani RA, Missotten L, Geboes K. Expression of CD23/CD21 and CD40/CD40 ligand in vernal keratoconjunctivitis. *Eye (Lond)* 2001;**15**(Pt 2):217–224.
31. Leonardi A, Curnow SJ, Zhan H, Calder VL. Multiple cytokines in human tear specimens in seasonal and chronic allergic eye disease and in conjunctival fibroblast cultures. *Clin Exp Allergy* 2006;**36**:777–784.
32. Leonardi A, Sathe S, Bortolotti M, Beaton A, Sack R. Cytokines, matrix metalloproteinases, angiogenic and growth factors in tears of normal subjects and vernal keratoconjunctivitis patients. *Allergy* 2009;**64**:710–717.
33. Shoji J, Inada N, Sawa M. Antibody array-generated cytokine profiles of tears of patients with vernal keratoconjunctivitis or giant papillary conjunctivitis. *Jpn J Ophthalmol* 2006;**50**:195–204.
34. Leonardi A, Brun P, Abatangelo G, Plebani M, Secchi AG. Tear levels and activity of matrix metalloproteinase (MMP)-1 and MMP-9 in vernal keratoconjunctivitis. *Invest Ophthalmol Vis Sci* 2003;**44**:3052–3058.
35. Manzouri B, Ohbayashi M, Leonardi A, Larkin DF, Ono SJ. Characterization of dendritic cell phenotype in allergic conjunctiva: increased expression of Fc(ϵ)RI, the high-affinity receptor for immunoglobulin E. *Eye (Lond)* 2009;**23**:2099–2104.
36. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M et al. Case series of 406 vernal keratoconjunctivitis patients: a demographic and epidemiological study. *Acta Ophthalmol Scand* 2006;**84**:406–410.
37. Kumagai N, Fukuda K, Fujitsu Y, Yamamoto K, Nishida T. Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. *Prog Retin Eye Res* 2006;**25**:165–187.
38. Motterle L, Diebold Y, Enriquez de Salamanca A, Saez V, Garcia-Vazquez C, Stern ME et al. Altered expression of neurotransmitter receptors and neuromediators in vernal keratoconjunctivitis. *Arch Ophthalmol* 2006;**124**:462–468.
39. Bonini S. Atopic keratoconjunctivitis. *Allergy* 2004;**59**(Suppl 78):71–73.
40. Nivenius E, Montan PG, Chrysanthou E, Jung K, van Hage-Hamsten M, van der Ploeg I. No apparent association between periocular and ocular microcolonization and the degree of inflammation in patients with atopic keratoconjunctivitis. *Clin Exp Allergy* 2004;**34**:725–730.
41. Yamagami S, Ebihara N, Amano SY. Chemokine receptor gene expression in giant papillae of atopic keratoconjunctivitis. *Mol Vis* 2005;**11**:192–200.
42. Dogru M, Okada N, Asano-Kato N, Igarashi A, Fukagawa K, Shimazaki J et al. Alterations of the ocular surface epithelial mucins 1, 2, 4 and the tear functions in patients with atopic keratoconjunctivitis. *Clin Exp Allergy* 2006;**36**:1556–1565.
43. Bonini S, Micera A, Iovieno A, Lambiase A. Expression of Toll-like receptors in healthy and allergic conjunctiva. *Ophthalmology* 2005;**112**:1528.

44. Thakur A, Willcox MD. Contact lens wear alters the production of certain inflammatory mediators in tears. *Exp Eye Res* 2000;**70**:255–259.
45. Vieira T, Lopes C, Pereira AM, Araujo L, Moreira A, Delgado L. Microarray based IgE detection in poly-sensitized allergic patients with suspected food allergy - an approach in four clinical cases. *Allergol Immunopathol (Madr)* 2012;**40**:172–180.
46. Mortemousque B, Fauquert JL, Chiambaretta F, Demoly P, Helleboid L, Creuzot-Garcher C et al. Conjunctival provocation test: recommendations. *J Fr Ophthalmol* 2006;**29**:837–846.
47. Leonardi A, Battista MC, Gismondi M, Fregona IA, Secchi AG. Antigen sensitivity evaluated by tear-specific and serum-specific IgE, skin tests, and conjunctival and nasal provocation tests in patients with ocular allergic disease. *Eye* 1993;**7**(Pt 3):461–464.
48. Bourke J, Coulson I, English J. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001;**145**:877–885.
49. Le Coz CJ, Sasseville D. Interpretation and relevance of patch testing: false-positive and false-negative test reactions, compound allergy, cross-sensitivity. *Ann Dermatol Venerol* 2009;**136**:610–616.
50. Leonardi A. In-vivo diagnostic measurements of ocular inflammation. *Curr Opin Allergy Clin Immunol* 2005;**5**:464–472.
51. Mimura T, Usui T, Mori M, Funatsu H, Noma H, Yamamoto H et al. Relation Between Total Tear IgE and Specific Serum IgE in Seasonal Allergic Conjunctivitis. *Cornea* 2011;**30**:790–795.
52. Batellier L, Poilane C, Rault J, Chaumeil C, Scat Y. Measurement of total IgE in tears: the adaptation of an immunoenzyme technique and the value of investigating locally produced IgE in the diagnosis of chronic conjunctivitis. *Ann Biol Clin (Paris)* 1999;**57**:469–473.
53. Leonardi A, Jose PJ, Zhan H, Calder VL. Tear and mucus eotaxin-1 and eotaxin-2 in allergic keratoconjunctivitis. *Ophthalmology* 2003;**110**:487–492.
54. Hu Y, Matsumoto Y, Adan ES, Dogru M, Fukagawa K, Tsubota K et al. Corneal in vivo confocal scanning laser microscopy in patients with atopic keratoconjunctivitis. *Ophthalmology* 2008;**115**:2004–2012.
55. Leonardi A, Lazzarini D, Bortolotti M, Pili-ego F, Midena E, Fregona I. Corneal Confocal Microscopy in Patients with Vernal Keratoconjunctivitis. *Ophthalmology* 2012;**119**:509–515.
56. Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs* 2005;**65**:215–228.
57. Abelson MB, McLaughlin JT, Gomes PJ. Antihistamines in ocular allergy: are they all created equal? *Curr Allergy Asthma Rep* 2011;**11**:205–211.
58. Verin P, Easty DL, Secchi A, Ciprandi G, Partouche P, Nemeth-Wasmer G et al. Clinical evaluation of twice-daily emedastine 0.05% eye drops (Emadine eye drops) versus levocabastine 0.05% eye drops in patients with allergic conjunctivitis. *Am J Ophthalmol* 2001;**131**:691–698.
59. Cook EB, Stahl JL, Barney NP, Graziano FM. Mechanisms of antihistamines and mast cell stabilizers in ocular allergic inflammation. *Curr Drug Targets Inflamm Allergy* 2002;**1**:167–180.
60. Yanni JM, Miller ST, Gamache DA, Spellman JM, Xu S, Sharif NA. Comparative effects of topical ocular anti-allergy drugs on human conjunctival mast cells. *Ann Allergy Asthma Immunol* 1997;**79**:541–545.
61. Borazan M, Karalezli A, Akova YA, Akman A, Kiyici H, Erbek SS. Efficacy of olopatadine HCl 0.1%, ketotifen fumarate 0.025%, epinastine HCl 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions for seasonal allergic conjunctivitis: a placebo-controlled environmental trial. *Acta Ophthalmol* 2009;**87**:549–554.
62. Ballas Z, Blumenthal M, Tinkelman DG, Kriz R, Rupp G. Clinical evaluation of ketorolac tromethamine 0.5% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol* 1993;**38**(Suppl):141–148.
63. Tauber J, Raizman MB, Ostrov CS, Laibovitz RA, Abelson MB, Betts JG et al. A multicenter comparison of the ocular efficacy and safety of diclofenac 0.1% solution with that of ketorolac 0.5% solution in patients with acute seasonal allergic conjunctivitis. *J Ocul Pharmacol Ther* 1998;**14**:137–145.
64. Bielory L, Chun Y, Bielory BP, Canonica GW. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. *Allergy* 2011;**66**:686–693.
65. Kaiser HB, Naclerio RM, Given J, Toler TN, Ellsworth A, Philpot EE. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;**119**:1430–1437.
66. Lightman S, Scadding GK. Should Intranasal Corticosteroids Be Used for the Treatment of Ocular Symptoms of Allergic Rhinoconjunctivitis? A Review of Their Efficacy and Safety Profile *Int Arch Allergy Immunol* 2012;**158**:317–325.
67. Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R et al. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002;**89**:298–303.
68. Utine CA, Stern M, Akpek EK. Clinical review: topical ophthalmic use of cyclosporin A. *Ocul Immunol Inflamm* 2010;**18**:352–361.
69. Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical ciclosporin A in steroid dependent allergic conjunctivitis. *Br J Ophthalmol* 2006;**90**:461–464.
70. Lambiasi A, Leonardi A, Sacchetti M, Deligianni V, Sposato S, Bonini S. Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study. *J Allergy Clin Immunol* 2011;**128**:896–897.
71. Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J et al. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2009;**25**:365–372.
72. Rikkers SM, Holland GN, Drayton GE, Michel FK, Torres MF, Takahashi S. Topical tacrolimus treatment of atopic eyelid disease. *Am J Ophthalmol* 2003;**135**:297–302.
73. Vichayanond P, Tantimongkolsuk C, Dumrongkigchaiporn P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P. Vernal keratoconjunctivitis: Result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment. *J Allergy Clin Immunol* 2004;**113**:355–358.
74. Attas-Fox L, Barkana Y, Iskhakov V, Rayvich S, Gerber Y, Morad Y et al. Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. *Curr Eye Res* 2008;**33**:545–549.
75. Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat* 2010;**21**:144–156.
76. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst Rev* 2011;**7**:CD007685.
77. Frolund L, Durham SR, Calderon M, Emminger W, Andersen JS, Rask P et al. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. *Allergy* 2010;**65**:753–757.
78. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy* 2011;**41**:1263–1272.