Allergic Conjunctivitis

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Abstract

Interest in allergic conjunctivitis (AC), isolated or associated to allergic rhinitis, has increased in recent years due to its high and growing prevalence, the important healthcare costs generated by the disease, and its impact upon patient quality of life. A review is made of the immunopathological mechanisms of AC, its diagnosis and the differential diagnosis with other ophthalmological allergic disorders. The current management of AC is based on minimizing contact of the causal allergen with the conjunctiva using a series of protective measures, and on controlling the symptoms produced by the allergic inflammatory process. A review is made of the different drug groups that can be used for the treatment of the symptoms, and of the role of specific allergen-based immunotherapy in the management of AC. Lastly, a review is made of the methodology used in performing conjunctival provocation tests, which are useful and necessary in some cases in order to establish the diagnosis, for assessing treatment response, and for investigating the physiopathological mechanisms underlying the conjunctival allergic inflammatory response.

Key words: Allergic conjunctivitis. Epidemiology. Immunopathology. Ocular allergy. Ocular allergy diagnosis. Ocular provocation. Treatment.

Resumen

El interés por la conjuntivitis alérgica (CA) aislada o asociada a rinitis alérgica ha aumentando en los últimos años, debido a su alta prevalencia y al incremento de ésta, a los importantes gastos sanitarios que genera y al impacto en la calidad de vida de los pacientes. Se han revisado los mecanismos inmunopatológicos, su diagnóstico y el diagnóstico diferencial con otras entidades de alergia ocular. El tratamiento actual de la CA se basa en evitar o minimizar el contacto del alérgeno con la conjuntiva, mediante una serie de medidas de protección y, por otro lado, en controlar los síntomas desencadenados por el proceso inflamatorio alérgico. Se han revisado los diferentes grupos farmacológicos que se pueden utilizar como tratamiento sintomático y el papel de la inmunoterapia específica con alérgenos en el tratamiento de la CA. Por último, se revisa la metodología empleada en la realización de la provocación conjuntival, prueba útil y necesaria en algunas ocasiones para el diagnóstico, para evaluar la respuesta al tratamiento y para investigar los mecanismos fisiopatológicos de la respuesta inflamatoria alérgica conjuntival.

Palabras clave: Conjuntivitis alérgica. Epidemiología. Inmunopatología. Alergia ocular. Diagnóstico alergia ocular. Provocación ocular. Tratamiento.

Introduction

According to the classification of ocular allergy proposed in 2006 by the International Ocular Inflammation Society (IOIS) [1] (Table 1), based on immunopathological mechanisms, allergic conjunctivitis (AC) is a type of ocular allergy which in turn can be subdivided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC). This classification also includes other conditions such as atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), giant papillary conjunctivitis (GPC) and contact dermatoconjunctivitis (CDC) – with different manifestations, different clinical courses, different immunopathological characteristics, and variable responses to treatment.

Table 1. Clinical and immunopathological classification of ocular allergy [1]

	IgE-mediated	IgE- and non- IgE-mediated	Non- IgE-mediated
Intermittent	SAC		
Persistent	PAC	VKC	GPC
Chronic		AKC	CDC

Abbreviations: IgE, immunoglobulin E; SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; CDC, contact dermatoconjunctivitis.

AC can affect both children and adults, often coexisting with other allergic diseases such as asthma, atopic dermatitis or food allergy, though it is particularly associated to allergic rhinitis. Indeed, the term "rhinoconjunctivitis" is used in joint reference to both disorders, thereby complicating knowledge of each individual disease condition. Nevertheless, in recent years new studies have made it possible to know the true prevalence of allergic conjunctivitis, its natural history and socioeconomic impact in the different countries.

Epidemiology

The epidemiology of ocular allergic diseases has not been sufficiently investigated to date. In general, ocular allergy is estimated to affect 5-22% of the population, depending on the geographical setting and on the age of the population studied [2].

In the United States, the *National Health and Nutrition Examination Survey III* (NHANES III) found that ocular symptoms, defined as "episodes of tearing and ocular itching", affected 40% of the adult population, with no significant differences according to age [3], though with a predominance in the south versus other regions of the country. Exposure to aeroallergens (animal epithelia, pollen and mites) triggered more ocular symptoms than nasal manifestations. Thus, during the months of May and August, in relation to the environmental pollen levels, ocular symptoms were seen to predominate over nasal symptoms. On examining the prevalence of ocular allergy in relation to the results of the skin tests made with the mentioned environmental aeroallergens [4], the authors found patients with AC to have greater skin reactivity than patients with allergic rhinitis.

In Italy [5], a study involving 898 new patients visiting an allergy clinic found 40% of the subjects to report symptoms compatible with AC, and 66% of them were also diagnosed with seasonal allergic rhinitis.

A Japanese study [6] in turn found 90% of all patients with pollen allergy to present AC.

Isolated conjunctivitis was diagnosed in 8% of a series of 509 Swedish patients with pollinosis, and in 6.7% of those with only rhinitis [7]. In reference to age, a bimodal presentation was noted, with a first peak at 15 years of age and a second peak at between 35-40 years of age. Likewise, it was estimated that the symptoms of conjunctivitis were at least as intense as the nasal symptoms in 70% of the patients. This study also found isolated conjunctivitis to be associated to asthma in 10% of the patients, versus in 32% in the case of rhinoconjunctivitis and in 35% in the patients with only rhinitis. Posteriorly, in that same country and based on a written questionnaire administered to children between 12 and 13 years of age, the cumulative prevalence of allergic conjunctivitis was estimated to be 19.1%, and was found to be associated to rhinitis in 92% of the cases [8].

In Spain, the Alergológica 2005 study [9] found rhinoconjunctivitis to be the main reason among children for consulting the allergologist. Specifically, 46.3% (425 patients out of a total of 917 studied subjects) consulted for this reason, and in 410 individuals (44.7%) the diagnosis was confirmed. The mean patient age was 9 years. Of the 390 children (95%) with symptoms of rhinitis, 61% also presented conjunctival symptoms. Only 20 children (5%) had isolated conjunctivitis.

Recently, a study has been made of the prevalence of AC in a population between 13-14 years of age in Curitiba (Brazil) [10], following the methodology of the ISAAC study [11], with a modification of the written questionnaire. In this study 17% of the subjects presented ocular symptoms, with a similar frequency in both sexes. All the patients with conjunctivitis also had rhinitis. The authors concluded that the validation of questionnaires addressing ocular symptoms could facilitate knowledge of the prevalence of conjunctivitis and its relation to other allergic diseases.

Quality of life and economical impact

Although AC is regarded as the most benign form of all ocular allergic conditions, it may limit patient quality of life – affecting daily life activities and psychosocial relations, and generating important economic costs that vary from one country to another, depending on the existing healthcare model and the characteristics of the study sample.

The quality of life of patients with AC can be affected by the intense itching, causing dryness sensation, vision fatigue and even reading difficulties. Different questionnaires, validated in the Spanish population, have been developed to explore different aspects of this disease:

- EQ-5D [12], examines the impact upon general health.
- OSDI [13], evaluates the degree of discomfort of the eye surface.
- VFQ-25 [14], explores vision.
- RQLQ [15], specific of rhinoconjunctivitis, and other abbreviated forms, the miniRLQLQ [16] and ESPRINT-15 [17].
- EAPIQ [18], evaluates the impact of ocular allergy upon the daily life activities of patients and the degree of satisfaction with the treatment received (not validated in the Spanish population).
- HEDQ [19], reports on health-related aspects from the economical and demographic perspective.

Regarding the direct and indirect costs of allergic conjunctivitis, few studies have measured the economical impact of this disease independently from allergic rhinitis. The study published by Pitt et al. [19] has been the first to relate economical cost and quality of life in a group of public healthcare patients with SAC during the pollinic season of 2002 in Oxfordshire, compared with a control group. This study estimated the annual cost per patient to vary between 64£ and 124£, with a reduction in productivity of 2.3 hours/week during the pollinic season. A similar study was carried out in Spain in 2003 [20]. In this case the patients corresponded to private centers, with an estimated cost of 348.50 €/year for each patient with SAC.

Physiopathology

Allergic conjunctivitis is a bilateral and self-limiting inflammatory process. The inflammation is fundamentally caused by an IgE-mediated immune mechanism or immediate hypersensitivity mechanism resulting from direct contact of the allergen with the conjunctival surface in sensitized patients – triggering mast cell activation and the release of different mediators. However, other mechanisms and mediators are also implicated in this inflammatory process, such as the neurogenic mechanism, adhesion molecules, and other systemic immune mechanisms that contribute to the appearance of the signs and symptoms that characterize the disease [21].

Immediate hypersensitivity mechanism

Antigen-presenting cells play a very important role in the initiation of the allergic inflammatory process. Some of them, such as the dendritic cells, appear to participate actively in AC; accordingly, the inhibition of these cells could be used as a treatment strategy to suppress the disease [22].

Once the allergen is presented together with the class II histocompatibility molecules to the CD4+ T helper lymphocytes (Th), the Th2 lymphocyte population expands and secretes a series of cytokines, which in turn promote specific IgE synthesis on the part of the B lymphocytes and another series of cytokines (IL-4, IL-13) that facilitate the growth and differentiation of these B cells [23].

The synthesized specific IgE in turn binds to the membrane of the conjunctival mast cells via specific high-affinity receptors (FcεRI). When a new contact with the allergen occurs, the latter binds to at least two specific IgE molecules, and the immediate allergic reaction response is triggered, with the release of different mediators. Some of these mediators are preformed and associated to granules, e.g., histamine, proteoglycans (heparin, chondroitin sulfate), neutral proteases (tryptase, chymase), acid hydrolases, or certain oxidative enzymes, while others are synthesized de *novo* – such as the lipid mediators (prostaglandins, leukotrienes), platelet factor (PAF), certain interleukins (IL-4, IL-5, IL-6, IL-8, IL-13), and tumor necrosis factor (TNFα). Posteriorly, the late response develops, dependent primarily on the recruitment and activation of eosinophils and T lymphocytes [24].

In SAC and PAC, development of the late phase varies among patients. In some cases the response follows the classical pattern, in which 4-8 hours after contact with the allergen the clinical symptoms reappear and a second peak in mediator concentration is observed, though in other cases the symptoms are continuous or intermittent. This variability appears to depend on the intensity of the immediate response. In this context, it has been observed that low-dose provocations lead to self-limited immediate responses, while high-dose provocations or provocations in highly sensitized individuals give rise to a more intense and prolonged response, with cell recruitment and the development of a late response [25]. Nevertheless, much research remains to be done to explore and explain the late response mechanisms in the eye, as well as their repercussions in future treatments [26].

Adhesion molecules

At present, the structural elements of the surface of the eye, such as the myofibroblasts and epithelial cells, are considered to play an important role in the modulation and development of ocular allergy. Specifically, the epithelial cells play a key role due to their capacity to synthesize cytokines [27], and because of expression of their adhesion molecules [21].

E-selectin elevation is observed about 30 minutes after exposure of the conjunctiva to an allergen to which the patient is sensitized, and after 4-24 hours increased expression is observed of both intercellular adhesion molecules (ICAM-1) required for eosinophil adhesion, and of vascular cell adhesion molecules (VCAM-1). This increase in adhesion molecules is observed in all types of AC [28].

Neurogenic mechanism

In the case of any type of ocular aggression, a local reactive release of neuromediators takes place, giving rise to a type of response known as neurogenic inflammation – defined as the inflammatory changes mediated by antidromic sensory nervous stimulation, and posteriorly by autonomic activation [29].

This neurogenic control, with interaction among the nervous, immune and endocrine systems, operates together with innate immunity to control and protect the surface of the eye. Although there is practically no activity under physiological conditions, the neuromediators – including neurotransmitters, neuropeptides and neurotrophins – are quickly released under disease conditions [30].

The neuropeptides, which act as mediators between the cells of the immune system and nervous system, and are present mainly in the aqueous humor, contribute to maintain the intraocular immune depression microenvironment. Their receptors may be present in neuronal and non-neuronal cells such as mast cells, eosinophils, epithelial cells and fibroblasts. Classically, some sensory neuropeptides such as substance P and CGRP (calcitonin gene-related peptide) have been implicated in pain transmission [31], though in recent years they have also been seen to play an important role in the pathogenesis of allergic response – contributing to tissue damage and its chronification [32]. Furthermore, they influence the Th1/Th2 phenotypic change and play a role in B lymphocyte immunoglobulin isotype change [33].

Vasoactive intestinal peptide (VIP) is found in parasympathetic nerves and in cells of the immune system. VIP is a neuropeptide that participates in the maintenance of immune tolerance in the development of the regulatory T cells, as well as in the Th1 to Th2 phenotypic change, and controls and regulates the activation of IgE expression in mast cells, and also mucin secretion control [34].

Another molecule, neuropeptide Y (NPY), is produced by sympathetic nerves and immune cells, and exerts a modulating effect upon the natural killer (NK) cells. It also intervenes in the regulation of Th1 response, in the distribution and migration of macrophages and T lymphocytes, and in immunoglobulin production on the part of the B lymphocytes, and in cytokine release [35].

Neuron growth factor (NGF), released by inflammatory cells (monocytes / macrophages, neutrophils), Th0/1/2 and B lymphocytes, and the nervous system, intervenes in the neurogenic inflammatory process of allergic phenomena [36], and appears to be able to regulate the endocrine and immune systems, modulating Th and B lymphocyte proliferation and stimulation [37]. In addition, NGF increases the functional activity of mast cells and eosinophils [38].

The production of tears and mucin is also regulated by the communication that exists between the sensory network and the sympathetic/parasympathetic system; accordingly, a patient can present ocular symptoms without direct exposure or aggression of the conjunctiva [39]. It has been observed that mechanical or chemical stimulation of the nasal mucosa induces tearing or lacrimation via the so-called nasal-ocular reflex [40]. Following unilateral nasal provocation with allergens, local histamine release takes place (along with other mediators such as substance P). The histamine binds to the H1 receptors of the afferent nerve endings of the nasal mucosa and sends signals to the mesencephalon through the trigeminal nerve. From here the lacrimal glands and mucin glands at nasal level are stimulated along the efferent pathway through the parasympathetic nerve endings which release acetylcholine. The end effect is an increase in vascular permeability and nasal-nasal reflex secretion, together with itching and bilateral tearing. The released histamine is local, since after unilateral nasal provocation the histamine levels are not found to be increased in the ocular secretions – thus indicating that there are no degranulated mast cells at this level. Histamine only appears elevated in the stimulated nasal passage – though the secretion volumes increase bilaterally.

The nasal-ocular reflex, which appears to be increased in allergic patients, serves as the basis for explaining the beneficial effect of nasal corticosteroids in relation to ocular symptoms relief [41].

Systemic immune mechanism

In cases of anaphylaxis due to the intake of food or medicines, insect bites or aeroallergen inhalation, the associated systemic immune response can also contribute to conjunctival inflammation. Thus, when an allergen is deposited in the nasal mucosa, it rapidly enters the systemic bloodstream and increases the activity of the circulating immune cells, with the elevation of IL-5 [42]. This leads to an alteration in the regulation of eotaxin levels and adhesion molecules (VCAM-1 and ICAM-1) at conjunctival level – with the resulting development of surface eosinophilic inflammation.

Clinical aspects and diagnosis

SAC is the most common form of all ocular allergic diseases, and is fundamentally triggered by exposure to pollen. Clinically, SAC is more often found in young adults between 20-40 years of age, with no gender predilection. The symptoms manifest particularly in spring, though this depends on the causal pollen and on the corresponding pollination date [43]. SAC is frequently associated to allergic rhinitis and asthma [44]. Involvement is usually bilateral, and the patients experience itching (the main symptom), as well as tearing and burning sensation. Blurred vision and photophobia can be observed in the more severe presentations. Blurred vision in AC can be due to an alteration in the composition and stability of the tear film in over 78% of all patients, as established from interferometric studies [45].

Among the clinical signs, it is possible to observe mild to moderate conjunctival hyperemia, with an edematous conjunctival surface. The palpebral conjunctiva appears pale pink in color, with a milky aspect, a whitish exudate and – in some cases – diffuse areas of slightly hypertrophic papillae, predominantly located in the upper tarsal conjunctiva. The cornea is rarely affected.

The diagnosis is confirmed by a family or personal history of atopic alterations, and positive skin tests in response to the suspect seasonal allergens. However, in some cases skin testing is not determinant, since some studies have found that up to 47% of all patients can show sensitization to perennial allergens [46]. Other studies have reported that over 24% of the patients can exhibit polysensitization [47], and in some cases of SAC the skin tests are even negative – particularly in the absence of associated rhinitis [48]. There are also other criteria that can help in establishing the diagnosis [49,50], such as the response to antiallergic treatment (topical antihistamines, topical mast cell stabilizers, multiple action drugs, etc.), serum IgE elevation (found in 78% of all patients with SAC – 69% being specific of pollen), lacrimal IgE elevation (in 96% of the patients), increased mast cell infiltration of the conjunctiva (in 61% of the cases), and increase in type T mast cells, with tryptase release in tears

following conjunctival provocation. Eosinophil infiltration in conjunctival swab samples has only been observed in 25% of all patients, and is not specific of SAC.

PAC is another form of AC usually induced by exposure to dust mites (in over 52% of all cases) [51], fungi, animal epithelial and/or occupational allergens. The affected patients can show symptoms throughout the year, though with exacerbations in 79% of the cases. No age or gender predilection is observed. It seems that the prevalence of association to perennial rhinitis or other allergic diseases is greater (over 95% of all subjects) [52] than in SAC, and a slight increase is also seen in the prevalence of eosinophils in conjunctival swab samples.

In some cases, establishing the etiological diagnosis of AC requires a conjunctival provocation test (see Annex I) [53-60].

This test can confirm allergen reactivity in the conjunctiva of patients with positive skin tests. However, the conjunctival provocation test is particularly useful in patients with negative skin tests or serum IgE determinations and a clinical history suggestive of AC, since it is possible to evaluate the local and specific response of the conjunctiva [61], as well as in polysensitized patients, with a view to defining the causal allergen [62].

Differential diagnosis

The differential diagnosis of AC must be established with other types of ocular allergy (AKC, VKC, GPC and CDC) that share symptoms in the form of itching, tearing and conjunctival hyperemia (reddening), and with other non-allergic ocular disorders (infections, autoimmune diseases) [49,62,63] (Tables 2, 3).

Table 2. Differential diagnosis of conjunctivitis

Allergic mechanism	Vernal keratoconjunctivitis Atopic keratoconjunctivitis Giant papillary conjunctivitis Contact dermatoconjunctivitis
Infectious mechanism	Viral conjunctivitis Bacterial conjunctivitis Fungal conjunctivitis Parasitic conjunctivitis
Autoimmune mechanism	Dry eye Scleritis Uveitis

Vernal keratoconjunctivitis (VKC)

VKC is a self-limiting, bilateral chronic inflammation that usually leaves no sequelae or permanent alterations in visual acuity, except in 5-6% of the patients [64]. It is more frequent in young males, with an increased incidence between 11-13 years of age, and shows no gender differences after puberty. VKC is rare in adults [65]. The symptoms may be seasonal or perennial, with exacerbations generally in summer or in early autumn.

Although the underlying cause is not known, genetic and environmental factors appear to be determinant (with a predominance in warm and dry climates). The etiopathogenesis is not precisely known, though two hypersensitivity mechanisms seem to be involved (type I and type IV) [66]. Accordingly, in the presence of an antigen, lymphocyte activation (predominantly of the Th2 subpopulation) would take place. An increased presence of goblet cells is observed in the conjunctiva, with an elevation of the MUC5AC levels, which may contribute to the abundant mucosal secretion observed in these individuals [67]. Conjunctival involvement can show two forms: palpebral, with giant subtarsal papillae (7-8 mm in diameter) showing a typical cobblestone pattern, with profuse mucus secretion (Figure 1), and limbal with Horner-Trantas dots, that appear as small gelatinous nodules at limbus level, and are typical of the active phase of the disease (Figure 2).

Corneal involvement can manifest as a *micropannus* (Figure 3) (vascularization of the cornea as a result of repeated inflammation of the latter), *superficial punctate keratopathy* (punctiform epithelial denudation normally located in the upper half of the cornea), *corneal macroerosions* and *shield ulcerations*, covered with mucus and fibrin plaques, *subepithelial scarring* and *pseudogerontoxon* (opacification of the cornea adjacent to the superior limbus).

Although one-half of the patients may also present other allergic problems such as asthma, rhinitis and eczemas, in 42-47% of the cases the skin tests and specific IgE determinations prove negative. Conjunctival biopsy reveals an increase in basophils, eosinophils, mast cells, plasma cells and lymphocytes that also appear in the smears. The tears show very high levels of histamine (due to a deficit of histaminase enzyme) [68], tryptase, eotaxin and eosinophil cationic protein, and increased adhesion molecules (VCAM-1) and leukotrienes (LTB4, LTC4).

Atopic keratoconjunctivitis (AKC)

AKC is a bilateral, chronic (though cyclic) inflammatory disorder of the conjunctiva that can have an important effect upon visual acuity. The underlying etiopathogenesis appears to involve type I and type IV hypersensitivity mechanisms, with the activation of type Th1 and Th2 lymphocytes [69], and a reduction in MUC5AC-secreting goblet cells [67].

While the disease can affect children, it is more common and serious in adults between 20-50 years of age, fundamentally in males [70]. There is a personal and family history of atopic disease in 95% of the cases. AKC is associated to rhinitis and asthma in 87% of the patients, and according to some studies, atopic dermatitis is present in 95% of the cases [71].

The eyelids usually have an eczematous appearance, together with chronic blepharitis. The chronic palpebral edema gives rise to a sign known as the "Dennie-Morgan fold", at infraorbital level.

Scratching may cause a loss of eyelashes on the external side, known as the "Hertoghe sign". These patients also show important susceptibility towards non-ulcerative blepharitis and palpebral infections due to *Staphylococcus*, meibomitis, trichiasis, ectropion and entropion.

Table 3. Differential diagnosis of ocular allergy. Adapted from Mantelli et al. [49]

	SAC	PAC	VKC	AKC	GPC	CDC
Personal/ family history of atopy	Common	Common	Possible	Constant	Possible	Possible
Age	Children/Adults	Children/Adults	Children	Adults	Adolescents/Adults	Adults
Gender	No predilection	No predilection	Males	Males	No predilection	No predilection
Seasonal	Spring	Perennial	Perennial/Summer	Perennial	Spring	No
Corneal involvement	No	No	Yes	Yes	No	No
Vision involvement	Minimal	Minimal	Mild	Severe	Minimal	Minimal
Papillary hypertrophy	No	No	7-8 mm Limbus affected	< 1 mm	> 1 mm	No
Periocular skin involvement	Edema	Edema	Edema	Dermatitis	Edema	Dermatitis
Exposure to topical drugs	No	No	No	No	No	Yes
Contact lens wearer	No	No	No	No	Yes	No
Serum IgE	Elevated	Elevated	Variable	Greatly elevated	Variable	Variable
Eosinophils in swabs	Frequent	Very frequent	Characteristic	Characteristic	Not frequent	Not frequent
Goblet cells	Increased	Increased	Increased	Decreased	Variable	Variable
Skin tests	Positive	Positive	Non-specific	Positive	Variable	Variable
Other atopic diseases	Rhinitis Asthma	Rhinitis Asthma	Variable	Dermatitis Asthma Rhinitis	Variable	Variable
Response to Antiallergic drugs	Characteristics	Characteristics	Low	Low	Variable	No
Response to Topical corticosteroids	Constant	Constant	Constant	Constant	Constant	Constant

Abbreviations: SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; CDC, contact dermatoconjunctivitis.

The conjunctiva shows a predominantly inferior tarsal reaction (in contrast to VKC), with papillary hypertrophy < 1 mm in diameter. Chronic conjunctival aggression can lead to corneal neovascularization and scaring conjunctivitis, with the appearance of symblepharon.

Chronic inflammation of the corneal surface can give rise to punctate epithelial keratitis, more evident in the lower third of the cornea, and which may progress towards corneal ulceration. Corneal involvement is more severe than in other forms of ocular allergy (VKC), and the development of severe pannus is common, and may even complicate the performance of a penetrating keratoplasty, if this operation proves necessary. Limbal infiltrates or Horner-Trantas dots may appear but are less frequent than in VKC.

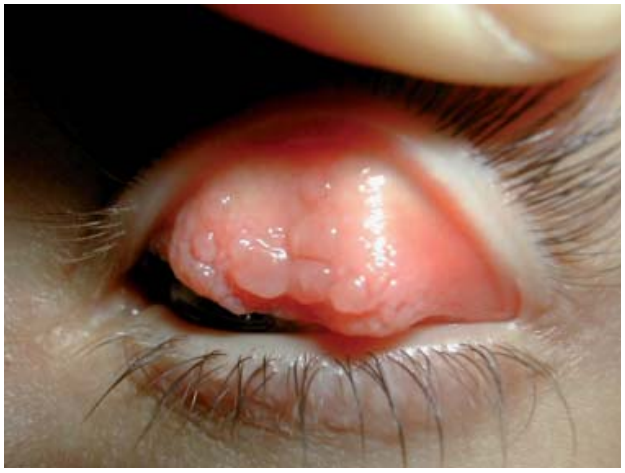

Figure 1. Giant hypertrophic papillae in vernal keratoconjunctivitis.

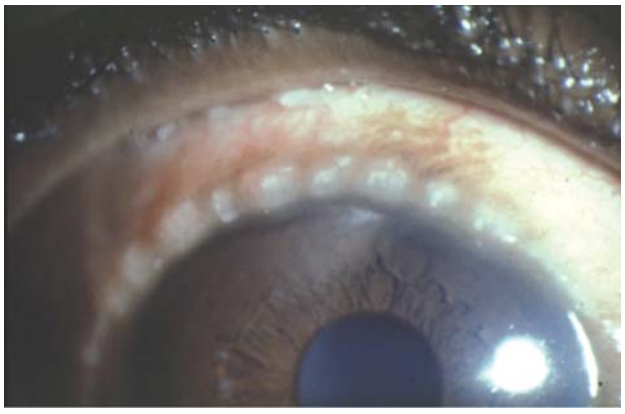

Figure 2. Horner-Trantas dots.

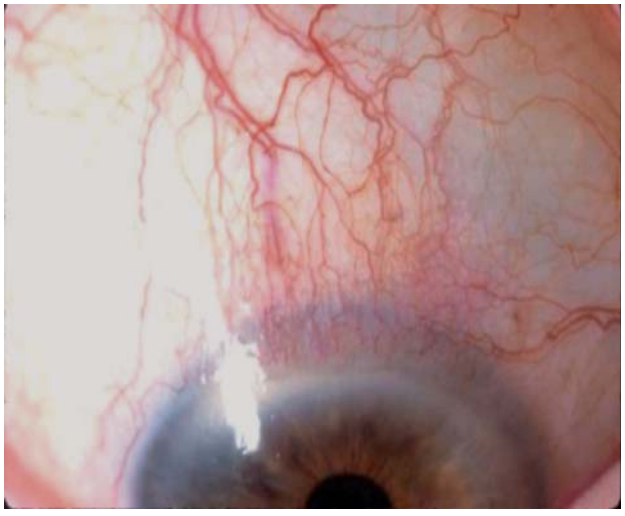

Figure 3. *Pannus* in the upper third of the cornea.

The immune system disorders usually found in these patients, together with the need for frequent corticosteroid treatments, increase the risk of certain infections such as herpetic keratitis or mycotic keratitis, and the appearance of posterior subcapsular cataracts and glaucoma. Likewise, a relationship has been described among AKC, the appearance of keratoconus, and retinal detachment.

Skin tests and specific IgE determinations can be useful for evaluating hypersensitivity to some allergens. Serum total IgE is usually increased, but is not correlated to the severity of the symptoms. The conjunctival smear reveals a large number of eosinophils. Tear samples also show elevations in eotaxin, eosinophil cationic protein, certain adhesion molecules, and even IL-5 (which shows good correlation to the severity of the condition). A conjunctival biopsy is sometimes needed to establish a differential diagnosis with other forms of cicatrizing conjunctivitis.

Giant papillary conjunctivitis (GPC)

GPC is a bilateral but asymmetrical, non-infectious inflammatory disorder of the surface of the eye, related to the wearing of contact lenses, ocular prostheses or sutures – although a genetic predisposition also appears to be involved [49]. The disorder affects 5-10% of all contact lens wearers, and is more common among individuals wearing soft lenses versus rigid or semi-rigid contact lenses. GPC can manifest at any age and shows no race or gender predilection. It can affect both atopic and non-atopic individuals, though the signs and symptoms are more severe among the former. Exacerbations are usually observed during the spring season. Dry eye is also considered to be a predisposing factor.

The etiopathogenesis of GPC [72] is thought to involve mechanical trauma to the conjunctiva and cornea, with the induction of alterations in local inflammatory mediators such as IL-8, and the recruitment of dendritic cells, which increase antigen presentation to the cells. Many substances can serve as antigenic stimulus: bacterial products, lubricating eyedrops, preservative solutions (thiomersal), disinfecting solutions (quaternary ammonium compounds), or even the contact lens material itself. An increased contact lens water content has been associated with increased protein uptake at lens surface level, and thicker and more irregular lens margins are correlated to an increased frequency of the disease. Exploration reveals the presence of giant papillae measuring over 1 mm in size in the superior tarsal conjunctiva, though in the early stages of the process the dimensions may be smaller. The cornea can also be affected in the form of punctate keratitis occasionally manifesting with peripheral infiltrates, corneal neovascularization, and sometimes also limbus involvement [49].

Contact dermatoconjunctivitis (CDC)

CDC is a form of contact dermatitis that affects the conjunctiva and the eyelids. It can manifest in both atopic and non-atopic individuals.

CDC results from a type IV late hypersensitivity reaction in which the T cells interact with haptens (incomplete antigens), which are converted into complete and immunogenically active antigens upon binding to other proteins [63]. These antigens

in turn are taken up by the Langerhans cells of the skin of the eyelid or conjunctiva, and are presented to the T helper lymphocytes in the regional lymph nodes. The sensitized T cells release cytokines and chemotactic factors, with the consequent activation of inflammatory cells. Sensitization may develop in weeks or months, depending on the allergen concentration, the existence of previous disease of the eyelids or conjunctiva, and on inherent patient susceptibility.

In sensitized individuals, the immune response takes 48-72 hours to develop, in contrast to toxic or irritative reactions, which manifest within 2-3 hours.

Many products can act as antigens:

- Mydriatic drugs: atropine, homatropine, tropicamide, scopolamine.
- Antibiotics: aminoglycosides, sulfamides, polymyxin.
- Antiviral agents: idoxuridine, trifluridine, vidarabine.
- Anti-glaucoma agents: carbachol, brimonidine, apraclonidine, dorzolamide.
- Preservatives: thiomersal, benzalkonium chloride, chlorhexidine, EDTA.
- Anesthetics: procaine, tetracaine.
- Others: phenylephrine.
- Cosmetics (nail varnish, rimmel, lipstick), soaps, detergents.

The early stages are characterized by involvement of the lower conjunctiva, followed by the eyelid and finally the rest of the conjunctiva and the upper eyelid. The acute phase may show blepharitis of an acute eczematous appearance, while the chronic phase is characterized by the appearance of folds, crusts and fissures, with thickening of the skin.

At conjunctival level [69] it is possible to observe papillae, follicles, pseudopemphigoid lesions and pseudotrachomas. The cornea can be affected in the form of superficial punctate keratitis, with the generation of marginal infiltrates, ulcers and even stromal edema.

The diagnosis of these eye conditions is initially based on the clinical findings, and is posteriorly supported by epicutaneous patch tests involving the suspect substances, with a view to identifying the causal allergen.

Treatment

The treatment of AC on one hand aims to prevent or minimize allergen contact with the conjunctiva, based on a series of protective measures (environmental control, cold water pads, eye lubricants without preservatives, contact lenses, etc.), and on the other hand to control the symptoms triggered by the allergic inflammatory process, administering different drug groups such as antihistamines, mast cell stabilizers, dual-action drugs (antihistaminic and mast cell-stabilizing action), non-steroidal antiinflammatory drugs (NSAIDs) and corticosteroids (Tables 4, 5). The role of specific immunotherapy targeted to the causal allergen in the management of AC has been the subject of study in recent years [73].

The present review offers some considerations regarding the pharmacological treatment of AC, based on systematic reviews and clinical trials, though in contrast to other allergic diseases, there are no international guides [74] or exhaustive and precise analyses capable of providing an orientation as to which treatment is most adequate, not only in terms of efficacy/adverse events, but also quantifying psychosocial factors, patient preferences or costs. Nevertheless, Bielory recently conducted a review on some of the treatments used in application to the nasal and ocular symptoms, with the definition of a series of levels of evidence [75].

Table 4. Treatment of allergic conjunctivitis

Non-pharmacological	Allergen-avoidance Cold pads Artificial lubricants	
Pharmacological		
Topical ocular	Antihistamines	Antazoline Pheniramine Levocabastine Emedastine
	Vasoconstrictors	Oxymetazoline Naphazoline Tetrahydrozoline Phenylephrine
	Mast cell stabilizers	Sodium cromoglycate Lodoxamine NAAGA
	NSAIDs	Ketorolac Pranoprofen Fluribuprofen Diclofenac
	Multiple action	Olopatadine Ketotifen Nedocromil Azelastine Epinastine
	Corticosteroids	Medroxyprogesterone Fluormetholone Dexamethasone Prednisolone Clobetasone Rimexolone Loteprednol
Oral	Antihistamines	Cetirizine Loratadine Ebastine Mizolastine Desloratadine Levocetirizine Fexofenadine Rupatadine Bilastine
Topical nasal	Corticosteroids	Fluticasone Mometasone

Inmunotherapy: Subcutaneous, sublingual

Abbreviations: NSAIDs, non-steroidal antiinflammatory drugs; NAAGA "N-acetyl-aspartyl glutamic acid or spaglumic acid".

Table 5. Topical treatment for allergic conjunctivitis

Drug	Dose
Emedastine	Age ≥ 3 years 1 drop every 6 hours
Levocabastine	Age ≥ 12 years 1 drop every 6 hours
Cromoglycate	Age ≥ 2 years 1 drop every 6 hours
Lodoxamide	Age ≥ 2 years 1-2 drop every 6 hours
NAAGA	Age ≥ 3 years 1-2 drop every 6 hours
Ketorolac	Age ≥ 12 years 1 drop every 6 hours
Olopatadine	Age ≥ 3 years 1-2 drop every 12 hours
Epinastine	Age ≥ 3 years 1 drop every 12 hours
Azelastine	Age ≥ 3 years 1 drop every 12 hours
Ketotifen	Age ≥ 3 years 1 drop every 8 hours
Nedocromil	Age ≥ 3 years 1-2 drop every 12 hours
Rimexolone	Age ≥ 12 years 1-2 drop every 6 hours
Loteprednol	Age ≥ 3 years 1-2 drop every 6 hours

Topical ocular vasoconstrictors

These drugs are highly effective in reducing conjunctival hyperemia through their alpha-adrenergic stimulatory effect, though their action is limited in time (2-4 hours). The most commonly used are: oxymetazoline, naphazoline, tetrahydrozoline and phenylephrine. As side effects, the topical ocular vasoconstrictors can cause follicular conjunctivitis, eczematous blepharoconjunctivitis and drug induced conjunctivitis secondary to rebound hyperemia following prolonged administration. They are therefore not usually recommended for the treatment of AC. Caution is required when administering these substances to patients with glaucoma, hyperthyroidism and cardiovascular diseases [76]. They are usually combined with topical antihistamines [77]. Few studies have compared the different vasoconstrictors, and there are insufficient data to orientate towards the choice of one drug or other. Oxymetazoline is regarded as the most potent decongestant, with the fastest and longest-lasting action, compared with naphazoline and tetrahydrozoline [78].

Oral antihistamines

These drugs block the symptoms produced by histamine, as a result of interaction with the H_1 receptors present in the nerve endings (reducing itching sensation) and located in the blood vessels (reducing edema and vasodilatation) [73], though some of these substances also have antiinflammatory properties [79], with the inhibition of ICAM-1 expression, or effects upon PAF, among other actions.

The first-generation antihistamines are not recommended, due to their sedative effects and anticholinergic activities, while the second-generation drugs (cetirizine, desloratadine, levocetirizine, fexofenadine, loratadine, rupatadine, ebastine and mizolastine) are widely used to control the ocular and nasal symptoms of patients with rhinoconjunctivitis, in view of their lesser adverse effects – though their antimuscarinic action may lead to alterations in the tear film. Clinical trials have demonstrated the efficacy of these drugs versus placebo [80], but few trials have compared them among each other. In this context, rupatadine has been shown to be as effective as cetirizine [81] or loratadine [82] in affording ocular symptoms relief in adult seasonal allergic rhinoconjunctivitis. Ebastine in turn has been shown to be as effective as loratadine in affording ocular symptoms relief in patients with seasonal rhinoconjunctivitis [83], though in application to perennial rhinoconjunctivitis it is only been found to improve tearing [84]. Mizolastine showed greater improvement in the first three days of treatment than cetirizine [85]. Recently, bilastine has been presented as a new antihistamine affording efficacy and safety similar to that of desloratadine [86] and cetirizine [87]. At present there is insufficient evidence to recommend one oral antihistamine or other for the treatment of AC, and the choice should depend upon the individual characteristics of each patient.

Topical ocular antihistamines

The most widely used first-generation topical ocular antihistamines are antazoline and pheniramine. They are administered for AC symptoms relief associated to topical vasoconstrictors, though in view of the above mentioned adverse effects, they are not regarded as adequate long-term treatment [88]. The new generation of topical antihistamines, such as 0.05% levocabastine and 0.05% emedastine, are superior to the first-generation drugs.

Levocabastine is a selective H_1 receptor antagonist. Its efficacy and safety in application to AC has been assessed in a metaanalysis [89] selecting 9 randomized, double-blind and placebo-controlled studies. On comparing the improvement of the ocular symptoms in patients with seasonal rhinoconjunctivitis, the effect was seen to be similar to that of loratadine [90] and superior to that of terfenadine, in controlling ocular itching [91].

Emedastine is regarded as a relatively selective H_1 receptor antagonist, with some added antiinflammatory action, that has demonstrated its efficacy versus placebo in the prevention and treatment of AC [92]. Compared with levocabastine, this drug has been shown to be more effective in the prevention and treatment of AC in adults and children over four years of age [93].

Topical ocular mast cell stabilizers

Sodium cromoglycate (SCG) is regarded as the prototype mast cell degranulation-inhibiting drug, though it does not act upon the type T mast cells. At a concentration of 4%, its efficacy has been demonstrated versus placebo in the treatment of AC [94], and its regular use proves more beneficial than when administration is carried out upon demand [95]. The drug has been found to be less potent than levocabastine in conjunctival provocation models [96].

As a mast cell stabilizer, lodoxamide is considered to be 2500 times more potent than sodium cromoglycate. Lodoxamide is able to reduce the tryptase levels and inflammatory cell recruitment towards the ocular fluid [97], as well as reduce ICAM-1 expression [98] and the levels of histamine, in both immediate and in late reactions [99]. Its efficacy versus placebo has been demonstrated [100], and the drug is as effective as levocabastine [101] in patients with AC. Compared with sodium cromoglycate, it has been shown to be more potent, faster acting, and with fewer adverse effects [102].

NAAGA (N-acetyl-aspartyl glutamic acid or spaglumic acid), regarded as a mast cell membrane stabilizer, acts by inhibiting leukotriene synthesis. It is faster acting than sodium cromoglycate [103], but slower than lodoxamide [104].

Topical ocular non-steroidal antiinflammatory drugs (NSAIDs)

These drugs block the cyclooxygenase pathway; as a result, they reduce prostaglandin and thromboxane synthesis. The marketed topical agents (0.5% ketorolac, 0.1% diclofenac, 0.5% pranoprofen and 0.03% flurbiprofen) have demonstrated their efficacy in a metaanalysis, in application to itching and conjunctival hyperemia [105] versus placebo, though no efficacy studies comparing the different drugs among each other have been carried out.

Ketorolac at a concentration of 0.5% has been found to be superior to levocabastine [106], but less effective than emedastine in application to itching in ocular provocation models [107]. There have been some reports of asthmatic crises after the topical administration of ketorolac; as a result, it should not be used in asthmatic patients with NSAID intolerance [108].

Topical ocular drugs with antihistamine and mast cell stabilizing action

Olopatadine acts as a mast cell stabilizer and is also a selective H_1 receptor antagonist. Its efficacy versus placebo has been demonstrated in relation to improvement of the signs and symptoms of AC [109]. The drug acts rapidly and its effect is prolonged – possibly due to its capacity to suppress mediator release and inhibit inflammatory cell recruitment. Compared with sodium cromoglycate, olopatadine is more effective against SAC in patients under 11 years of age, and offers superior local tolerability [110]. It is also more effective than levocabastine [111] and ketorolac [112], in conjunctival provocation models.

Ketotifen at a concentration of 0.025% is able to stabilize the mast cell membrane and block the H1 receptors. It is superior to sodium cromoglycate in affording symptoms relief in conjunctival provocation models [113]. Experimental studies in animals have shown ketotifen to be more effective than olopatadine and levocabastine in reducing edema and vascular permeability [114], though in humans a significantly greater proportion of patients prefer olopatadine versus ketotifen, due to reasons of efficacy and convenience of use [115].

Sodium nedocromil at a concentration of 2% in ophthalmic solution is a stabilizer of the membranes of both types of mast cells (T and TC), but also has other properties, including H_1 receptor antagonism and the inhibition of mast cells and eosinophils [70]. Its efficacy versus placebo has been demonstrated in controlling the ocular symptoms of SAC [116]. Compared with other drugs such as ketotifen [117], olopatadine [118], levocabastine [119] and emedastine [120], sodium nedocromil is less effective and causes more discomfort after instillation.

Azelastine is a competitive H_1 receptor blocker that inhibits the release of histamine and of other both immediate and late phase allergic response mediators. Its efficacy versus placebo has been demonstrated in relation to symptoms control in SAC [121] and PAC [122]. Compared with olopatadine, the drug has afforded less relief from ocular itching in AC [123], though with effects similar to those of levocabastine in a pediatric population [124].

Epinastine at a concentration of 0.05% is a potent H_1 and H_2 histamine receptor antagonist with mast cell membrane stabilizing activity and the capacity to inhibit cytokine activation. Epinastine clearly reduces ocular itching compared with placebo [125], though in comparative studies with olopatadine, the latter proved more effective in alleviating itching and conjunctival hyperemia [126].

Intranasal corticosteroids

The role of the intranasal corticosteroids in improving the ocular symptoms of patients with allergic rhinitis has been the subject of debate in recent years [127]. The second-generation oral antihistamines were initially considered to be more advisable for controlling the ocular symptoms [128]. However, Weiner et al. [129], in a metaanalysis comparing oral antihistamines with intranasal corticosteroids (beclomethasone dipropionate, budesonide, fluticasone propionate and triamcinolone acetonide), concluded that there is no significant difference between the two groups in relation to the ocular symptoms. Posteriorly, another metaanalysis reported similar results comparing intranasal corticosteroids with topical antihistamines [130].

The effect of some intranasal corticosteroids upon the ocular symptoms, compared with placebo, has been demonstrated in several metaanalyses and for different corticosteroids: intranasal fluticasone propionate [131], mometasone furoate [132] and fluticasone furoate [133], and although in the case of other intranasal corticosteroids such as ciclesonide no effects have been recorded at this level [134], the existing clinical data indicate that the decrease in ocular symptoms with intranasal corticosteroids may represent a class effect, and that the variability of response is dependent upon the glucocorticoid receptor affinity of the drug in question [135].

Topical ocular corticosteroids

Topical ocular corticosteroids are used to treat the more severe and chronic forms of AC. When administered via the topical route these are the most potent antiinflammatory agents, because they interfere with intracellular protein synthesis and block phospholipase A_2 – the enzyme responsible for the formation of arachidonic acid. They also inhibit cytokine production and inflammatory cell migration. A number of different corticosteroids are available, with different potencies (from greater to lesser potency): medroxyprogesterone, fluorometholone, dexamethasone and prednisone.

The corticosteroids are potentially capable of causing important adverse effects, such as cataract formation, raised intraocular pressure and infections. These drugs must be used for short periods of time of no more than two weeks.

Dexamethasone, prednisolone and fluorometholone are corticosteroids with a ketone group in carbon 20, and are associated to cataract formation and the elevation of intraocular pressure. Although not yet authorized in Spain, a new molecule derived from prednisolone has recently been developed, loteprednol etabonate, in which the ketone group in carbon atom 20 has been replaced by an ester group with a minimum potential to cause ocular hypertension, due to its rapid conversion to an inactive metabolite [136]. This drug has been recommended by the guides and has been approved by the FDA for limited use in the more severe cases of SAC.

Another ophthalmological corticosteroid, rimexolone, has been shown to offer antiinflammatory potency similar to that of prednisone and dexamethasone, without elevating intraocular pressure. Its antiinflammatory action is due to the high lipophilicity of the drug molecule and its low water solubility. Its molecular structure allows for selective tissue action within the eye, exhibiting low affinity for the trabecular tissue. Rimexolone has demonstrated its usefulness in AC [137].

Inmunotherapy

The role of immunotherapy as primary treatment for AC has not been sufficiently investigated to date. On analyzing the clinical data obtained in patients with rhinoconjunctivitis who have received such therapy, the latter is evidently seen to be effective in application to the ocular symptoms [138]. However, the designs of most of these studies do not allow us to establish whether the ocular response is greater or lesser than the nasal response. Nevertheless, there are publications that identify the ocular signs and symptoms in separate categories [139], both in subcutaneous immunotherapy [140,41] and in sublingual immunotherapy [142], and it has even been seen that efficacy in relation to the ocular symptoms persists years after completing the administration of immunotherapy [143]. A recent metaanalysis [144] of 42 clinical trials has concluded that sublingual immunotherapy compared with placebo is moderately effective in reducing total and individual ocular symptom scores in subjects with rhinoconjunctivitis or AC. There is a need for further large rigorously designed studies that study long-term effectiveness after discontinuation of treatment and establish the cost-effectiveness of sublingual immunotherapy.

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ANNEX 1

CONJUNCTIVAL PROVOCATION TEST

1. Introduction

Conjunctival provocation has been one of the tests classically used to in relation to allergic manifestations. Blackley [53] employed the technique in 1870 to determine how certain pollens cause conjunctivitis, and years later Noon [54] considered "ophthalmic reaction" as a marker for measuring the "efficacy" of immunotherapy. In 1932 Peskin [55] used conjunctival provocation for the diagnosis of SAC, in those cases where the skin tests and patient history proved negative or doubtful. In this same line, Tuft et al. [56] performed over 7000 conjunctival provocation tests with aeroallergens (domestic dust, epithelia), and found them to be useful and safe for confirming the diagnosis of AC, even when the patient history and skin test readings were doubtful. Thus, the conjunctival provocation test is regarded as an in vivo model allowing us to evaluate the ocular response to exposure to a given allergen.

The validity of the test depends on the following:

- Sensitivity and specificity, which also depend on the quality of the substances used.
- Reproducibility; a rigorous technique therefore must be used both in performing the test and in evaluating the response.
- Safety, taking into account the pertinent protective measures in each case.

Before starting the test, the patient must sign the corresponding informed consent form. This is a document that can vary in terms of format from one center to another, though in all cases it at least must offer an explanation of how the test is made and of the possible risks, and must include a section with the personal data of the patient and his or her express consent and signature [57].

2. Indications

The ocular provocation test can be used for a number of purposes:

- To explore the ocular physiopathological mechanisms in situations of allergen exposure, in both the acute and late phase, and to identify and determine the importance of the mediators released during the allergic reaction.
- To either confirm or refute the implication of a given allergen in the ocular and/or systemic allergic manifestations, with a view to establishing an etiological diagnosis.
- To contribute to the pharmacological investigation of new molecules. The FDA regards ocular provocation as the only reference technique for the validation of molecules with ocular antiallergic action [58].
- To follow-up on and control the efficacy of immunotherapy.

3. Contraindications

- Any allergic disorder under unstable conditions (asthma, rhinitis, urticaria, etc.).
- Patients with heart disease and a contraindication to noradrenalin use, and subjects with severe arterial hypertension.
- Uncontrolled hyperthyroidism.
- Pregnancy.

4. Conditions prior to ocular provocation

- Avoid the following medication:
  - Oral antihistamines up to 7 days before the test, except ketotifen, which should be interrupted three weeks before.
  - Systemic corticosteroids, which are to be suspended two weeks before provocation testing.
  - Topical eyedrops containing any drug substance, which are to be suspended at least two days before testing.
- Avoidance of allergen exposure:
  - Ocular provocation testing with allergens must be carried out in the absence of antigenic stimulation, and checking (through ophthalmological examination) that there are no clinical signs or symptoms at ocular level.
  - A one-week interval must be observed between two successive ocular provocation tests.
  - Two provocation tests with different allergens in one same session (one in the right eye and the other in the left eye) is not considered valid.

5. Equipment and material required

- Standardized, stable, freeze-dried antigen extracts that can be prepared immediately before provocation testing, in water-soluble form and without preservatives.
- Extracts of natural origin are not recommended, except in special cases such as latex or occupational allergens.
- Pipettes for dispensing the volume of study substance.
- Frontal illumination (headlamp).
- Healthcare personnel trained to deal with any emergency situation, with the provision of adrenalin, antihistamines, bronchodilators, corticosteroids, etc.

6. Description of the technique

The reference technique for conjunctival provocation testing was described by Abelson in 1990 [59]. It involves placing a dose of the study allergen every 15 minutes on the external lower angle of the bulbar conjunctiva of one eye. The same amount of physiological saline solution is deposited on the contralateral eye, and serves as control.

6.1 Dose

The minimum and maximum doses deposited at ocular level vary among different authors [60], in the same way as progression of the dilutions, which vary according to a factor of 2, 3 or 10.

6.2 Volume instilled

The initial protocols proposed an allergen volume of 40 µl. However, taking into account that the maximum volume admitted by the eye is 30 µl, the French GOA group [60] estimates that 20 µl is the optimum volume for ocular provocation testing.

6.3 Clinical criteria

Following the model of Abelson [59], four clinical criteria are regarded as useful for assessing the result of conjunctival provocation testing: itching, reddening or hyperemia, tearing and edema or chemosis. Examination of the conjunctiva is to be carried out before provocation testing, and again 10-15 minutes after the administration of each dose. The test is considered to be positive when the sum of the values of each criterion is ≥ 5. If the sum of the criteria is < 5, the test is considered negative, and the next doses are successively applied until a positive response is obtained, or until the maximum dose is reached.

Pruritus (itching)

This is the first clinical symptom which the patient may report, and is due to H_1 receptor stimulation of the nerve endings. Itching can manifest from the third minute of ocular provocation, reaching a maximum after 5-15 minutes. The discomfort begins to subside after 20 minutes. The clinical response is scored by the patient: 0 = none, 1 = mild (intermittent itching sensation), 2 = moderate (permanent itching, without the need to rub the eyes), 3 = severe (permanent itching, with the need to rub the eyes), and 4 = very severe (unbearable sensation with an imperative need to rub the eyes).

Reddening

Reddening of the eye or hyperemia is due to the vasodilatation caused by stimulation of the H1 and H2 receptors of the vascular endothelium cells. It manifests after 5 minutes, reaching peak intensity after 20 minutes, and begins to subside after about 30 minutes. Evaluation is made by the physician, observing the vascularization at ciliary, episcleral and conjunctival level: 0 = none, 1 = mild (perhaps localized within some quadrant), 2 = moderate (more marked and diffuse reddening in the quadrants), and 3 = severe (very marked and diffuse reddening in the quadrants).

Tearing

Evaluation is made by the physician: 0 = none, 1 = mild (slightly humid eye), 2 = moderate (some tears), and 3 = intense (profuse tearing).

Chemosis

Evaluation is made by the physician: 0 = none, 1 = mild (conjunctiva raised from the sclera, detectable with a headlamp), 2 = moderate (visually evident, conjunctiva raised in the inferior zone), and 3 = severe (swollen conjunctiva).

6.4 Paraclinical criteria [61]

A number of immune markers can experience modifications after conjunctival provocation:

Histamine

The histamine levels in tears can be measured using enzyme immunoanalysis (ELISA) with a commercial kit. Histamine in tears appears elevated immediately after ocular provocation, as a result of massive mast cell degranulation, though it is quickly degraded by histaminase enzymes. The measurement of histamine is used especially for studying the mast cell stabilizing potential of different drugs.

Tryptase

Tryptase in tears is measured with the fluoroenzyme immunoassay technique (UNICAP) for studying the mast cell stabilizing potential of different drugs administered via the topical route.

Eosinophil cationic protein

Eosinophil cationic protein (ECP) is a marker correlated to the degree of eosinophil activation. It is significantly elevated in all forms of allergic conjunctivitis, particularly in the more severe presentations, and is usually detected 6 hours after ocular provocation.

Citokines

The determination of cytokine or adhesion molecule levels is not used for diagnostic purposes, though it proves useful in studies of allergic physiopathology and of the efficacy of antiallergic agents.

Prostaglandins and leukotrienes

Chromatographic and immunoassay studies have demonstrated increased prostaglandin D2 and leukotrienes C4, D4 and E4 in tears, following ocular provocation, though with important interindividual variations.