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Treating the Ocular Component of Allergic Rhinoconjunctivitis and Related Eye Disorders

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Abstract

Context

Allergy symptoms that affect the eyes are common in adults and children worldwide, and are often associated with nasal allergy symptoms, prompting the term ‘rhinoconjunctivitis’ to describe the condition. However, this condition has not always been recognized, and earlier literature reported allergic conjunctivitis only within a subset of nasal allergy patients.

Evidence Acquisition

To assess the current state of ocular allergy epidemiology, pathophysiology, and currently available treatment options, we performed a MEDLINE search for articles regarding ocular allergy, rhinoconjunctivitis, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC).

Evidence Synthesis

The more severe forms of ocular allergy are not only distressing, but can also threaten a patient's vision. Each type of ocular allergy is associated with ocular redness, itching, and tearing; however, AKC and VKC can threaten the cornea, and research has revealed that involvement of different immune cell populations (mast cells, eosinophils, and lymphocytes) may cause these more severe symptoms. A variety of treatment options exist to control ocular allergy symptoms. Nonpharmacologic options include allergen avoidance and lubrication with saline, and if these fail to be sufficiently effective, symptom relief may be provided by medicinal

agents that are either applied topically to the eye or taken orally. Recent evidence suggests that nasal allergy treatments applied topically to the nose may also positively affect ocular allergy symptoms, which raises the interesting possibility that a parasympathetic nasal-ocular neural reflex pathway may be involved in the stimulation of allergic responses in the eye.

Conclusions

Ocular allergy is underdiagnosed and has a significant impact on the life of the patient. It is vital to reach a better understanding of ocular allergic mechanisms and inflammation, which may lead to improved treatment.

Introduction

The incidence of allergies in developed countries has been increasing in recent years.[1–4] Although a single cause of this increase cannot be pinpointed, experts are considering the contribution of numerous factors, including genetics, air pollution in urban areas, pets, and early childhood exposure to infections. As more of the population require treatment for allergies, the associated costs have increased substantially.[5] Ocular allergy, which is often overlooked in the presence of asthma and nasal symptoms, can itself produce irritating symptoms and severe forms such as atopic keratoconjunctivitis could lead to visual loss.

Epidemiology of Ocular Allergy

Allergy is a common hypersensitivity disorder that affects 15% to 20% of the population in the western world,[6,7] and its prevalence is increasing worldwide. In the United States, ocular allergies are known to affect more than 20% of the general population[7] and in the United Kingdom, a prevalence of 18.2% has been reported.[6] The combination of allergic nasal and ocular symptoms (rhinoconjunctivitis) is extremely common in adults[7] and children. The International Study of Asthma and Allergy in Childhood (ISAAC) has shown that the prevalence of rhinitis with itchy-watery eyes varied between countries from 0.8% to 14.9% in 6- to 7-year-old children and from 1.4% to 39% in 13- to 14-year-old children (Figure 1).[8] However, it is not clear whether the prevalence of rhinitis and conjunctivitis were similar or if 1 symptom was more common than the other. There is a paucity of international data evaluating the prevalence of ocular allergies within adult populations; however, the incidence of nasal allergy has been determined to be 24% to 29%, 28% to 34%, 13% to 23%, 12% to18%, and 13% to 17% in the United Kingdom, France, Germany, Spain, and Italy, respectively,[9] and 14% in the United States.[10] A recent analysis of US Third National Health and Nutrition Examination Survey (NHANES III) data has shown that ocular symptoms, defined as ‘episodes of watery, itchy eyes,’ affected 40% of the adult population of the United States during a 12-month period, and prevalence of ocular symptoms did not change significantly with age.[11] The survey showed that cat exposure triggered ocular, nasal, or ocular and nasal symptoms in about one fifth of sufferers.[11] Household dust and pollen were the most common trigger for combined ocular and nasal symptoms across all regions of the country,[11] although household dust was a greater trigger for ocular symptoms in the South compared with other regions of the United States.[12] Ocular symptoms are also increasingly prevalent in Eastern countries; in Mongolia,

allergic rhinoconjunctivitis was found to affect 9.3%, 12.9%, and 18.4% of the population surveyed in villages, rural towns, and cities, respectively.[13] In Pakistan, allergic conjunctivitis (AC) affected 3.7% of the surveyed village population.[14] A study in Thailand, involving 445 patients with a history of ocular symptoms or suspected AC, was performed to analyze the clinical features, risk factors, and clinical course of various types of AC among Thai people.[15] Patients were evaluated by slit-lamp evaluation and a skin-prick test; 81.8% were diagnosed with perennial allergic conjunctivitis (PAC), 4.7% with AKC, 10.6% with VKC, and 2.9% with GPC. The mean age of onset of AC was 20.3 years, and the most common trigger was house dust. Patients with PAC were most commonly sensitized to house-dust mites (*Dermatophagoides pteronyssinus*) (70.2%), house dust (67.5%), cockroaches (44.3%), grass (42.2%), and insects (29.2%).[15]

Traditionally, allergy investigations have focused on nasal symptoms; however, recent studies have highlighted the prevalence and significance of ocular symptoms. Evidence suggests that ocular symptoms are particularly prevalent in seasonal allergic rhinitis (SAR) sufferers,[16] and in accordance, the NHANES III survey showed that during the summer months (May to August) in the United States, isolated ocular symptoms were more prevalent than isolated nasal symptoms[11] (Figure 2). Another study found that the incidence of conjunctivitis was high in patients experiencing allergic rhinitis (AR) in response to cypress pollen (approximately 88%).[17] Furthermore, an investigation of hay fever sufferers showed that ocular symptoms were experienced alone (8%) or in combination with nasal symptoms (85.3%) more often than nasal symptoms without conjunctivitis (6.7%).[18] This study also concluded that ocular symptoms were as severe or more severe than nasal symptoms in approximately 70% of patients.[18]

Ocular symptoms are not only common, but also distressing for sufferers. Over 50% of nasal allergy sufferers stated that watering and red/itching eyes were moderately to extremely bothersome in the recent Allergies in America survey,[10] and for 15% of sufferers the ocular component of the allergic hypersensitive reactions was the most bothersome symptom. Similarly, seasonal allergic conjunctivitis (SAC) sufferers have been shown to have a significantly reduced quality of life score as determined by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) compared with age-matched non-SAC patient controls.[19] SAC sufferers also score significantly lower than controls who do not suffer from ocular allergy symptoms in several domains of the Visual Functioning Questionnaire 25 (VQF-25), including mental health, social function, and overall vision.[19,20]

It is not known why the combination of symptoms varies among allergic patients; however, the reported symptom variation may arise from underestimation of the association between rhinitis and conjunctivitis in epidemiologic studies. Several signs of involvement of the external eye can be documented only with an accurate eye examination, which is not part of the protocol in most studies of rhinitis patients.[8] Moreover, several forms of conjunctivitis of varying severities exist, which may complicate assessments. A standardized format that integrates immunopathophysiology and symptom severity is yet to be developed; however, recent studies have used a measurement of ocular symptoms called the Total Ocular Symptom Score

(TOSS), which integrates individual ocular symptom components including itching, redness, and tearing.[21–23] In addition, some AR patients may not suffer from ocular symptoms as a result of more efficient washing mechanisms in the eye than the nose, or less contact with the allergen. Indeed, ocular washing mechanisms can vary between individuals, as demonstrated by the changing tear flow rate and composition observed with age.[24,25]

Economic Burden

The healthcare costs related to AR, including those for rhinoconjunctivitis, have been reported to be $5.9 billion in the United States, with medication use accounting for 25% of the costs (approximately $1.6 billion).[5] Of the $1.58 billion spent on prescription medication for AR in 1996, second-generation antihistamines accounted for 51%, intranasal corticosteroids (INS) 25%, and first-generation antihistamines 5%.[26] Prescription medication costs attributable to ocular allergy have increased substantially in the past decade to more than $200 million, and these costs are predicted to increase by approximately 25% per year.[5] Current expenditure in the United States is therefore likely to be approximately $500 million. The total number of prescriptions for ocular allergy in the United States has increased in parallel with these costs by a rate of 20% per year. In 2000, 30% of these prescriptions were written by primary care providers, while a further 50% could be attributed to eye care and allergy specialists (41% and 9%, respectively).[5]

In Europe, a study based in the United Kingdom estimated that the healthcare costs for an employed person with SAC totaled £124 per year, of which £46 could be attributed to medication.[19] Interestingly, SAC sufferers were significantly more likely to be unemployed than controls.[19] A Spanish study found the direct cost of SAC to be 151 Euros per patient, with medication costs totaling 68 Euros.[20] The associated costs of reduced productivity were higher, equating to 198 Euros.[20] In combination, these studies suggest that ocular allergy may cause a significant economic burden.

Pathophysiology

Allergic eye disease represents a spectrum of disorders, comprising SAC, PAC, AKC, VKC, and GPC. GPC is not always included in this grouping as it is caused by physical trauma and is typically associated with use of ‘extended wear’ soft contact lenses, although patients with a history of allergy may be at greater risk.[27] Of these ocular allergy types, SAC and PAC are the most common, although the proportion of the more severe forms of ocular allergic disease (AKC, VKC, and GPC) increase in countries in the southern hemisphere.[28] This could be due to increasing levels of industrialization and pollution or, alternatively, may be an anomaly arising from under-reporting of milder conditions.[28]

Common ocular clinical features of SAC, PAC, AKC, and VKC include redness, itching, and tearing.[29,30] The most striking difference within this group of ocular diseases is that SAC and PAC remain self-limited without ocular surface damage, while AKC and VKC can compromise the cornea, causing ulcers and scarring, and can ultimately lead to vision loss.[29,31] A study of 6 VKC and 13 AKC patients demonstrated that the severity of corneal damage was related

to conjunctival injection and edema, which are signs of inflammation,[32] while other studies have shown some correlation with cellular infiltrates and mucous discharge on the upper tarsal conjunctiva.[33,34] The differing involvement of right and left eyes in patients also indicates that local inflammatory factors are controlling the severity of these diseases. Due to the severity of AKC and VKC, it is important to identify the responsible inflammatory mediators and differentiate them from those responsible for SAC and PAC.

SAC and PAC are well defined by their initiation by an immunoglobulin E (IgE)-mediated mast-cell response (Figure 3), which leads to the production of mediators including histamine, leukotriene C_4 (LTC_4), and prostaglandin D_2 (PGD_2).[35] This early phase response peaks at approximately 20 minutes post-allergen exposure, and is followed by a late-phase response that peaks at approximately 6 hours, and is characterized by upregulation of adhesion molecules and increased mast cells, neutrophils, eosinophils, macrophages, and basophils in conjunctival biopsies.[36]

SAC is thought to be primarily mast-cell driven[37]; however, in addition to the mast-cell response, output of cytokines by conjunctival epithelium T cells leads to multiple cytokine appearance in tears in SAC. T cells also release cytokines in VKC and AKC.[38] Cytokine profiles have been shown to vary between diseases, and indicate a role for Th2 cells in VKC and a greater involvement of Th1 cells in AKC. T cells isolated from GPC-patient conjunctival biopsies, however, produced low amounts of cytokines.[39] Conversely, other studies have shown that cytokine profiles in tears of AKC,[40] and SAC, AKC, and VKC[38] patients support the involvement of mixed helper T cell populations in each disease type. The more prominent role of T cells in the pathogenesis of VKC and AKC is supported by the finding that greater numbers of these cells infiltrate the conjunctiva than in cases of SAC/PAC.[41]

A role for other conjunctival cells, such as epithelial cells and fibroblasts, has been suggested in many forms of conjunctival disorders but particularly in VKC since these cells produce elevated amounts of eotaxin-1 (an eosinophil chemoattractant) in VKC patients. Tear eotaxin-1 levels correlate with the involvement of the cornea in the disease process,[42] and infiltration of eosinophils into the conjunctiva is thought to lead to corneal lesions seen in VKC.[43] Although conjunctival eosinophil numbers have been shown to be raised above normal levels in a study of VKC, AKC, and GPC patients, GPC (which does not lead to corneal involvement) displayed the highest eosinophil infiltration, indicating that eosinophil numbers in the conjunctiva per se are not related to corneal involvement, but rather their state of activation.[44] However, a more recent study has found no eosinophil infiltration into the tarsal conjunctiva (the site at which the characteristic papillary reaction of GPC occurs) in GPC patients.[45] VKC and AKC, but not GPC, are associated with raised expression of several surface antigens of eosinophils in the conjunctiva,[44] which suggests that the level and type of activation of these cells are indicative of disease progression. Furthermore, conjunctival eosinophil granule major basic protein (MBP) has been shown to be raised in AKC patients, while both neutrophil elastase and MBP were raised in conjunctiva of VKC patients, which also indicates a role for neutrophils in this disease.[46] MBP, and also eosinophil cationic protein, have been shown to both reduce viability and affect the morphology of human corneal epithelial cells in vitro.[43] In combination,

these data show that although there is still some debate about the pathogenesis of each disease type, steps have been taken toward identifying the cellular mediators that lead to disease progression in the severe forms of ocular allergy. These mediators may provide targets for new treatments aimed at preventing the associated severe discomfort and blindness experienced by a subset of patients.

Treatment Options for Ocular Allergy

A range of treatment options are available for the control of ocular allergy symptoms, some of which may obviate pharmacologic interventions (Table 1). Allergen avoidance is implemented by minimizing patient contact with the allergens to which they are sensitive; however, the eyes present a large surface area and thus it is often impossible or at least impractical to avoid ocular exposure to airborne allergens. Allergens can also be diluted and removed from the ocular surface through lubrication with artificial tears (saline combined with a wetting and viscosity agent); however, the unit-dose packaging required for sterility makes these products expensive, and they do not treat the underlying allergic response. Cold compresses are another nonpharmacologic intervention that may provide relief from ocular symptoms.

When avoidance and nonpharmacologic strategies do not provide adequate symptom relief, pharmacologic treatments may be applied topically (Table 2) or given systemically to diminish the allergic response. For example, the H_1 topical antihistamine levocabastine hydrochloride is effective in rapidly relieving ocular inflammation when administered topically to the eye.[47,48] However, a limited duration of action necessitates frequent dosing of up to 4 times per day,[49] and topical antihistamines may be irritating to the eye, especially with prolonged use. Because atopy has been shown to be related to a fivefold increase in symptoms during allergy seasons, patients who use contact lenses should consider the use of soft daily-disposable lenses for comfort.[50] A small percentage of patients may have to discontinue the use of contact lenses during acute periods.

Combination treatments using decongestants with antihistamines have been shown to be more effective,[51] and are administered to the eye as drops up to 4 times daily. Decongestants (oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, and naphazoline hydrochloride) act primarily as vasoconstrictors and are effective in reducing erythema[51]; however, adverse effects include burning and stinging on instillation, mydriasis, and rebound hyperemia or conjunctivitis medicamentosa with chronic use.[52] Therefore, these treatments are suitable only for short-term symptom relief, and are not recommended for use in narrow-angle glaucoma patients.

Mast-cell stabilizing medications (cromolyn sodium 2% or 4%, lodoxamide tromethamine 0.1%, nedocromil sodium 2%) can also be applied topically to the eye, and may be suitable for more severe forms of conjunctivitis. However, for mast-cell stabilizers to be effective, the mast cell has to be de-activated before the allergic reaction is triggered, thus they require a loading period during which they must be applied before the antigen exposure. Compliance is, therefore, an important factor because frequent regular dosing before an allergic reaction can become difficult for patients to adhere to. Cromolyn sodium is used in several types of

become difficult for patients to adhere to. Cromolyn sodium is used in several types of conjunctivitis, including forms of AC; however, studies have shown only marginal effectiveness compared with placebo.[53–55] Lodoxamide tromethamine is more potent than cromolyn sodium in the prevention of histamine release in animal models,[56] and has been shown to provide relief from the symptoms of VKC.[57] Nedocromil sodium has also been shown to be more potent than cromolyn sodium.[58,59]

In contrast to classical mast-cell stabilizers, the topical antihistamine mast-cell stabilizers have a dual mode of action: they inhibit mast-cell degranulation while competitively blocking histamine binding to H_1 receptors, thus providing rapid allergic symptom relief through antihistamine action. As a result of this more rapid action, compliance is likely to be greater compared with that of the pure mast-cell stabilizers. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are possible candidates for treating the symptoms of SAC. The only NSAID currently approved for SAC is ketorolac tromethamine 0.5%, which works on the arachidonic acid cascade and is effective in reducing ocular itching. However, as is the case for several classes of topical ocular treatments, NSAIDs are also known to cause discomfort on instillation,[60–62] which may affect patient compliance.

The more severe variants of conjunctivitis, including AKC, VKC, and GPC, can be controlled by topical corticosteroids (loteprednol etabonate 0.2% and rimexolone 0.1%), which are also effective in the treatment of acute and chronic forms of AC.[63–66]. Corticosteroids administered via eye drops are associated with serious adverse events when administered over long periods, including increased intraocular pressure (IOP) and cataract formation, and these agents are therefore appropriate for short courses (up to 2 weeks); however, if needed for longer durations, an eye examination should be carried out, including baseline assessment of cataracts and IOP.[8]

The topical ocular treatments described above share common limitations that arise from the mode of administration. Many adults have poor tolerance of eye drops, and they are particularly difficult to administer in a sterile manner when patients suffer from arthritis or tremors, or when used in pediatric practice. Since eye drops are cleared rapidly from the eye, efficacy and duration of action may be reduced, necessitating frequent administration and increasing expense. Moreover, compliance is a major issue in the use of eye drops,[67,68] which may be exacerbated by allergies that affect multiple systems. Patients may need to use a nasal treatment plus oral antihistamines, and topical creams and inhalers. It may be beneficial to reduce the number of agents used regularly by a patient through the use of immunotherapy, and orally or nasally administered allergy treatments that are effective against ocular symptoms.[69]

The efficacy of immunotherapy against ocular symptoms precipitated by conjunctival antigen challenges was originally demonstrated in 1911,[70] and this well-established method may be considered for the long-term control of AC. Although some more recent studies have focused on nasal rather than ocular symptoms,[71] others have confirmed the efficacy of immunotherapy against ocular symptoms.[72–77] However, immune responses to allergen administration are not predictive of the effectiveness of the therapy,[78] and the therapy itself

can produce systemic reactions, the incidence and severity of which vary dependent on the type of allergen administered.[79] Traditionally, immunotherapy has involved subcutaneous administration of allergen solution; however, newer sublingual immunotherapy (SLIT) provides a more convenient option. SLIT requires further evaluation for ocular allergy relief; it has been shown to control ocular signs and symptoms,[80–82] although ocular symptoms may respond less well than nasal symptoms.[83]

Oral antihistamines (cetirizine hydrochloride, desloratadine, fexofenadine hydrochloride, and loratadine) are commonly used for the therapy of nasal and ocular allergy symptoms. These newer second-generation antihistamines are recommended in preference to first-generation antihistamines because they have a reduced propensity for adverse effects such as somnolence.[8] Loratadine has been shown to have a protective effect in conjunctival provocation tests,[84] and desloratadine[85] and fexofenadine hydrochloride[86,87] have been found to significantly reduce ocular symptoms of SAR in placebo-controlled studies. In addition, cetirizine has demonstrated efficacy against symptoms of AC in conjunctival provocation tests;[88,89] however, a double-blind placebo-controlled trial showed no impact on ocular symptoms of perennial allergic rhinitis (PAR).[90] Second-generation antihistamines can, however, induce ocular drying,[91,92] which may impair the protective barrier provided by the ocular tear film and thus actually worsen allergic symptoms. It has therefore been suggested that the concomitant use of an eye drop may treat ocular allergic symptoms more effectively.[31] Indeed, ketotifen fumarate plus desloratadine,[93] and olopatadine hydrochloride plus loratadine[94] have been shown to be more effective than either antihistamine alone as a result of the local effect of the topically applied agent. In addition, one trial has shown that eye irritation was significantly reduced by an antihistamine preparation that had been formulated for intranasal application (azelastine hydrochloride).[95] However, these results have been inconsistent because eye watering was significantly reduced compared with placebo by twice-daily (but not once-daily) application of azelastine hydrochloride in 1 trial,[96] but was not significantly reduced in another.[95]

Intranasal corticosteroids (INS) are highly effective for treating nasal symptoms of AR,[8] but the evidence that they may also be effective for the treatment of ocular symptoms is inconsistent. Currently, the mechanism by which intranasal treatments act on ocular symptoms is not known. Potential mechanisms include improved drainage of ocular secretions resulting from a reduction of edema and inflammation around the lower end of the nasolacrimal duct, and a decrease in neuronal reflex activity. It is well established that allergen challenges to one side of the nasal cavity lead to nasal secretion in the contralateral cavity via a neurologic reflex.[97–101] Nasal challenges have also produced ocular itching in 90% of patients in 1 study,[102] and ocular symptoms in approximately 20% in another,[103] suggesting that ocular symptoms may be induced by a nasal-ocular reflex (Figure 4). It may be the case that INS inhibit the nasal-ocular component of ocular allergy symptoms, but not the direct ocular component.

The variation in effectiveness of INS on ocular symptoms may therefore be the result of varying levels of affinity for nasal receptors. Systemic effects are unlikely with these agents as they

have low bioavailability and rapid first-pass metabolism leading to low plasma levels.[104,105] Thus, the amount of an intranasal steroid available in the eye for a direct therapeutic effect is miniscule. Passage of agents from the nose to the eye via the nasolacrimal duct has also been shown to be unlikely.[106] A number of large clinical trials have investigated the ocular efficacy of INS in allergic patients; a meta-analysis of 16 randomized controlled trials showed that INS were more effective against several nasal symptoms of AR than oral antihistamines, and also found no difference in efficacy against AR ocular symptoms between the treatment classes.[107] Similar conclusions were drawn by a systematic review that determined that 9 of 10 AR studies showed no difference in efficacy for ocular symptoms between INS and oral antihistamines, while 1 study showed superiority of the oral antihistamine.[108] In contrast, pooled efficacy data from 7 multicenter, randomized, double-blind, placebo-controlled studies have shown that the INS fluticasone propionate 200 mcg once daily provides effective relief of ocular symptoms associated with SAR.[22] In accordance, a randomized, double-blind, parallel group study conducted at 14 investigative sites showed that fluticasone propionate 200 mcg once daily significantly decreased the ocular symptoms score compared with vehicle placebo[21]; however, other placebo-controlled trials found no effect of fluticasone propionate on eye symptoms in adults[109] or children[110] with SAC.

Another nasally administered corticosteroid, triamcinolone acetonide, has also been shown to have efficacy against ocular symptoms; however, only 1 placebo-controlled trial showed a statistically significant improvement,[111] and these findings have not been consistent.[112] Similarly, a pooled analysis of 4 studies found that mometasone furoate 200 mcg once daily may also provide relief from ocular symptoms in patients with SAR.[23,113] In a recent study,[114] ciclesonide did not have a significant effect on non-nasal symptoms, or the eye symptom domain of the RQLQ.

Summary

Ocular allergies, which are often underdiagnosed, have a significant impact on the life of the patient. These symptoms are expensive in terms of treatment and also in terms of indirect costs. It is vital to reach a better understanding of allergic mechanisms and inflammation, which may lead to improved treatment. Moreover, the emergence of new medications for the treatment of nasal and ocular symptoms may improve compliance in patients suffering from allergic conditions, such as AR, in which the ocular component is present. Currently, the most effective treatments for AR are INS; it would be advantageous, therefore, to develop a drug of this class that is consistently shown to improve eye symptoms (as well as nasal symptoms) to provide greater symptom relief, increase patient compliance, and reduce costs associated with the current requirement for multiple medications.

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Figures and Tables

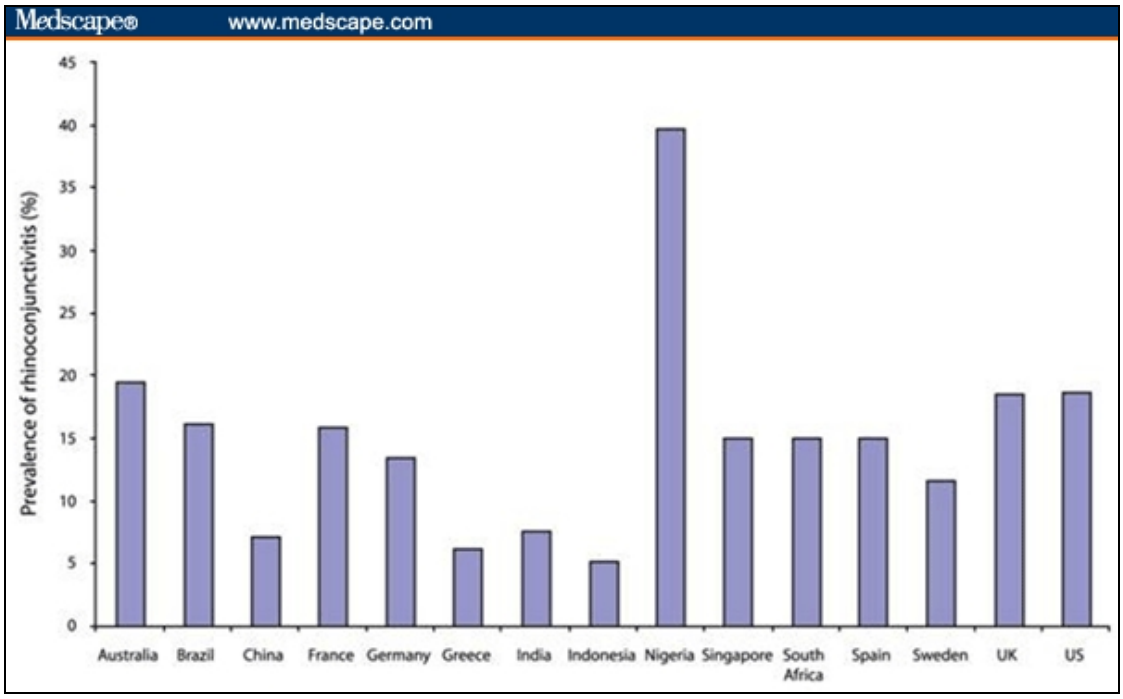

Figure 1

Prevalence of rhinoconjunctivitis in children aged 13–14 years from a selection of countries worldwide. Data from the International Study of Asthma and Allergies in Childhood (ISAAC) study.[115]

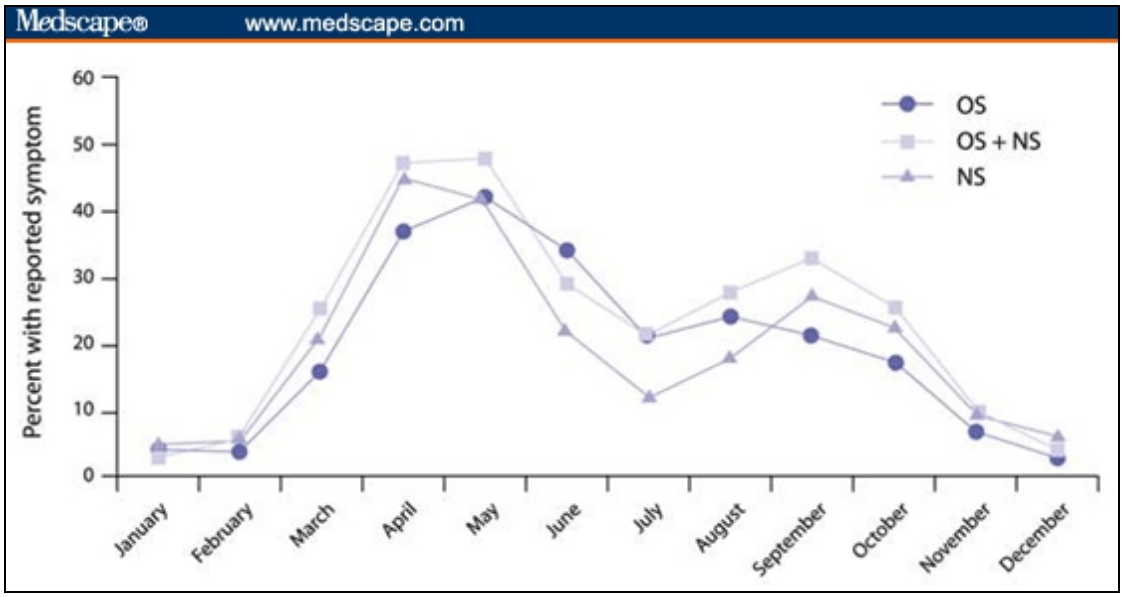

Figure 2

Comparison of symptoms exacerbated by pollen in the US adult population (US Third National Health and Nutrition Examination Survey; NHANES III). OS, ocular symptoms; NS, nasal symptoms.[11]

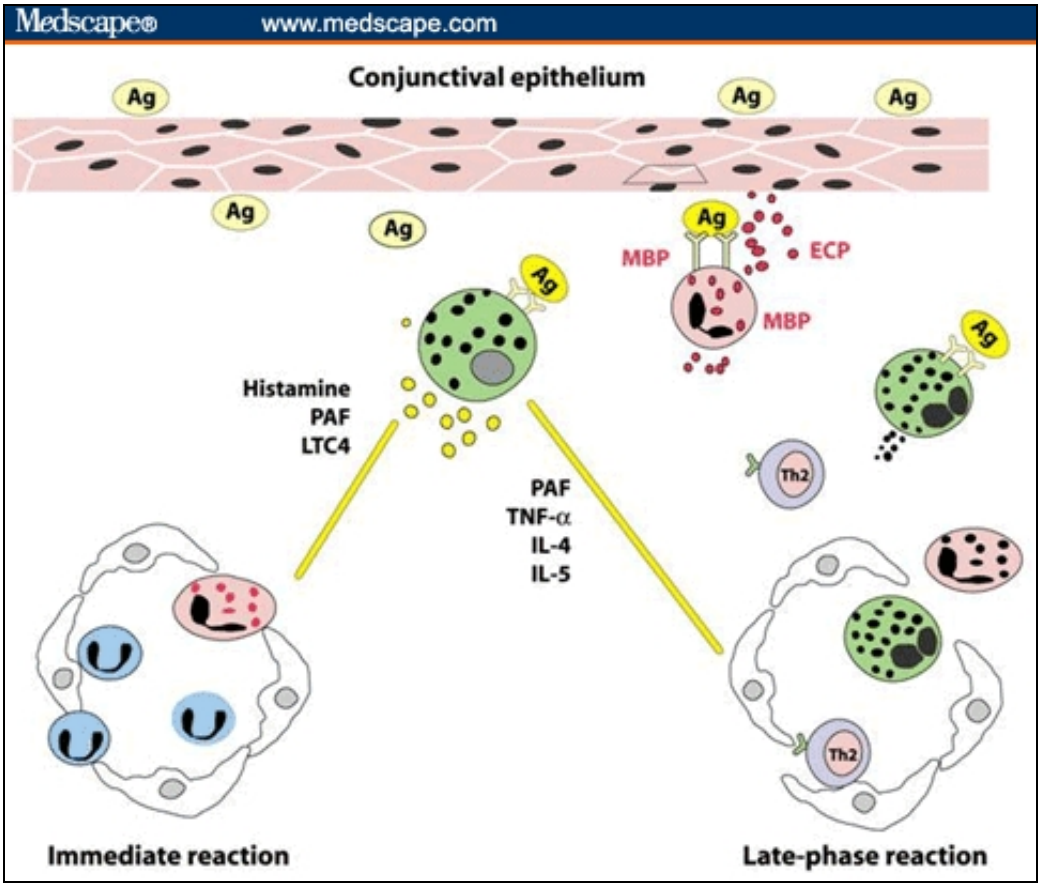

Figure 3

The immediate-phase reaction of seasonal and perennial allergic conjunctivitis is initiated by antigen binding to IgE on ocular mast cells, leading to degranulation and the release of histamine and other factors into the conjunctiva. The late-phase response involves mast cells, T cells and eosinophils, and peaks at approximately 6 hours post-allergen exposure. Ag, antigen; MBP, major basic protein; ECP, eosinophilic cationic protein; PAF, platelet-activating factor; LTC4, leukotriene C4; TNF-alpha, tumor necrosis factor-alpha; IL-4, interleukin-4; IL-5, interleukin-5; Th2, T-helper 2.

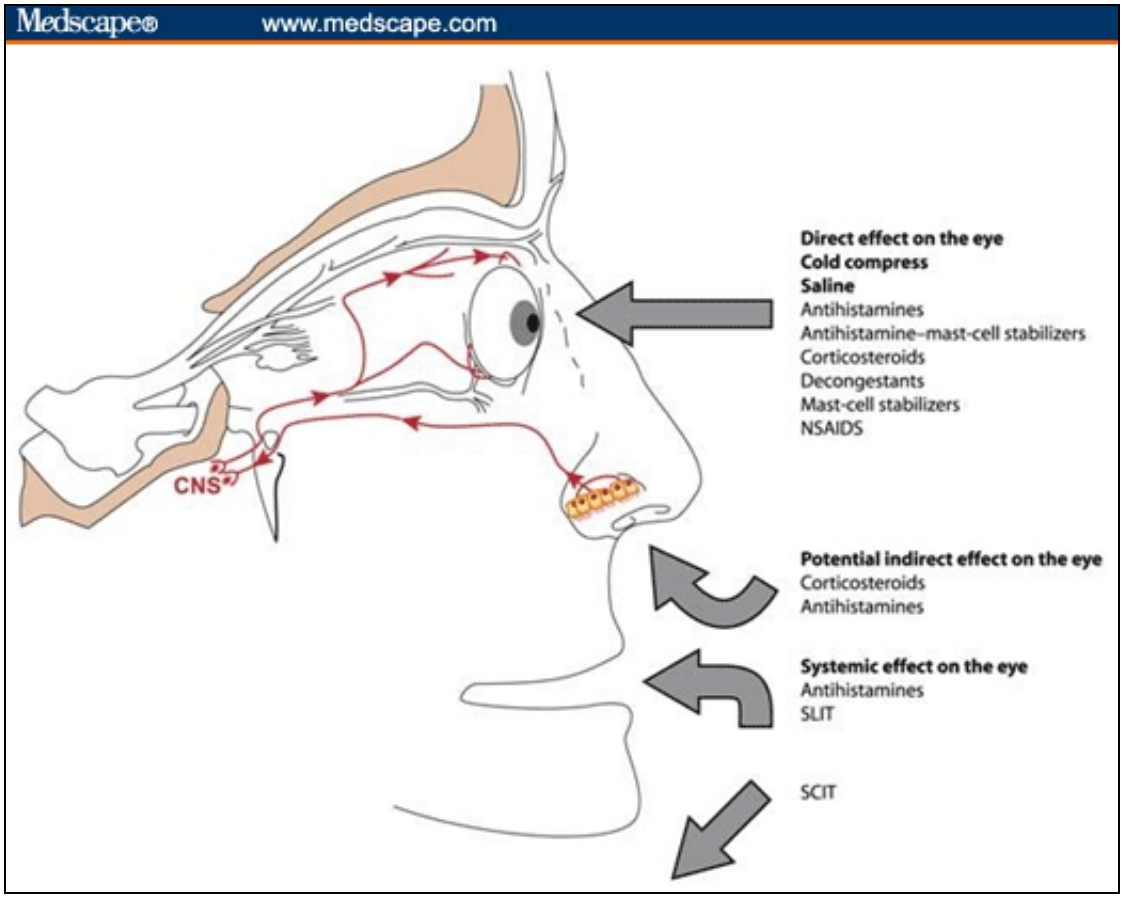

Figure 4

Routes of ocular allergy therapy administration. Nasal therapy may act on afferent nerve fibers to reduce the stimulation of ocular inflammation by efferent nerves in the hypothesized naso-ocular reflex. CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy.

Table 1

Therapy Options for Ocular Allergy

Nonpharmacologic		
	Allergen avoidance	
	Cold compress	
	Artificial tears	
Pharmacologic		
Topical	Antihistamine	Levocabastine hydrochloride, azelastine hydrochloride, pheniramine maleate
	Decongestant	Naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, tetrahydrozoline hydrochloride
	Multiple action antihistamine	Azelastine hydrochloride, emedastine difumarate, epinastine hydrochloride, ketotifen fumarate, levocabastine hydrochloride, olopatadine hydrochloride
	Mast-cell stabilizer	Cromolyn sodium, lodoxamide tromethamine, nedocromil sodium, pemirolast potassium
	NSAID	Ketorolac tromethamine
	Corticosteroid	Loteprednol etabonate, rimexolone, fluorometholone, prednisolone, dexamethasone
Sublingual / subcutaneous	Immunotherapy	
Oral	Antihistamine	Cetirizine hydrochloride, desloratadine, fexofenadine hydrochloride, loratadine, diphenhydramine hydrochloride, chlorpheniramine maleate, brompheniramine maleate, clemastine fumarate
	Decongestant	Pseudoephedrine
Nasal	Corticosteroid	Fluticasone propionate,* mometasone furoate*
	Antihistamine	Azelastine hydrochloride

NSAID, nonsteroidal anti-inflammatory drug;

*indicated for the management of nasal symptoms only

Table 2

Topical Ophthalmic Agents for Allergic Conjunctivitis

Generic (trade) name	Mechanism of Action	Dosage	Most Common Side Effects
Azelastine hydrochloride (*Optivar*)	Competes with H_1 receptor sites on effector cells and inhibits release of histamine and other mediators involved in allergic response	Age ≥ 3 y: 1 drop twice daily	Ocular burning (approx. 30%), Headache (approx. 5%), Bitter taste (approx. 10%)
Emedastine difumarate (*Emadine*)	Relatively selective histamine receptor antagonist	Age ≥ 3 y: 1 drop up to 4 times daily	Headache (11%)
Epinastine hydrochloride (*Elestat*)	Direct H_1-receptor antagonist, mast-cell stabilizer, inhibits cytokine activation	Age ≥ 3 y: 1 drop twice daily	Upper respiratory infection/cold symptoms (10%)
Ketorolac tromethamine (*Acular*)	Pyrrolopyrrole NSAID, inhibits prostaglandin synthesis	Age ≥ 12 y: 1 drop up to 4 times daily	Ocular burning, stinging, itching (10%)
Ketotifen fumarate (*Zaditor*)*	Noncompetitive H_1-receptor antagonist and mast-cell stabilizer	Age ≥ 3 y: 1 drop up to 3 times daily	Conjunctival injection, headache, rhinitis (10%–25%)
Levocabastine hydrochloride (*Livostin*)	Selective H_1-receptor antagonist	Age ≥ 12 y: 1 drop up to 4 times daily	Ocular burning, stinging, itching (10%)
Lodoxamide tromethamine (*Alomide*)	Mast-cell stabilizer	Age ≥ 2 y: 1–2 drops up to 4 times daily	Ocular burning, stinging, itching (10%)
Loteprednol etabonate (*Lotemax*, *Alrex*)	Decreases inflammation and late-phase response, decreases capillary permeability	Age ≥ 3 y: 1–2 drops twice up to 4 times daily	Headache (10%), pharyngitis (10%), rhinitis (10%)
Nedocromil sodium (*Alocril*)	Interferes with mast-cell degranulation, release of leukotrienes and platelet-activating factor	Age ≥ 3 y: 1–2 drops twice daily	Headache (10%), bitter taste (10%), ocular burning (10%), nasal congestion (10%)
Olopatadine	Selective H_1-receptor antagonist, inhibitor of	Age ≥ 3 y:	Headache (7%)

hydrochloride (*Patanol*)**	histamine release from mast cells, inhibits mediators from mast-cell fibroblasts and epithelial cells	1–2 drops up to 4 times daily

*Recently approved for over-the-counter use;

**_Pataday_ approved once a day treatment for ocular itching; reproduced with permission from Bielory L. *Ann Allergy Asthma Immunol*. 2007;98:105–115