

Developments in ocular allergy

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Purpose of review

The goal of this article is to evaluate developments in the knowledge of inflammatory mechanisms and treatments of ocular allergy.

Recent findings

Research developments in ocular allergy summarized in this article include the following findings: (1) ocular epithelial cells play a role in inflammation; (2) respiratory syncytial virus is a pathogen in allergic conjunctivitis; (3) transglutaminase inhibitors reverse allergic related inflammation; (4) eosinophils and neutrophils both play a role in ocular allergy; (5) eotaxin-1 and eotaxin-2 play a role in eosinophilic recruitment; and (6) loteprednol etabonate, desonide phosphate, and cyclosporine have been shown to be effective and safe in the treatment of ocular allergy.

Summary

This article summarizes the research conducted for each of the above recent findings and outlines their clinical applications.

Keywords

ocular allergy, seasonal allergic conjunctivitis, perennial allergic conjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, respiratory syncytial virus, eosinophils, neutrophils, major basic protein, CC-chemokine, loteprednol etabonate, desonide phosphate, cyclosporine

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Abbreviations

AKC	atopic keratoconjunctivitis
CCR	CC chemokine receptor
GPC	giant papillary conjunctivitis
MBP	major basic protein
PAC	perennial allergic conjunctivitis
PLA2	phospholipase A2
RANTES	regulated upon activation, normal T cell expressed and secreted
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
SAC	seasonal allergic conjunctivitis
TNF	tumor necrosis factor
VKC	vernal keratoconjunctivitis

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Introduction

The term ocular allergy encompasses several types of conjunctivitis, each of which affects individuals throughout the world. Based on the patient's presentation, conjunctivitis is divided into five subcategories, including seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC). These conditions are all caused by hypersensitivity reactions; however, AKC and VKC involve the cornea and potentially threaten vision, while SAC, PAC, and GPC are less severe.

Although a patient's signs and symptoms can be similar across some of these inflammatory reactions, it is important to be aware of the differences between them, including identification of the allergen, presence of inflammatory mediators, targets for treatment, and safe and effective treatment. The purpose of this review is to evaluate these aspects of ocular allergy

Seasonal and perennial allergic conjunctivitis

SAC and PAC are the most common types of ocular allergy. SAC is most commonly caused by familiar allergens such as ragweed and various pollens. It tends to occur most frequently during the seasons of spring and fall when levels of these irritants are high. PAC, however, is caused by more persistent allergens such as cat dander and dust mites; therefore, it is often more chronic than SAC.

Patients with both SAC and PAC often present with ocular itching, burning, tears, redness, and pain, which are all due to type I IgE hypersensitivity reactions. Phospholipase A2 (PLA2) is important in allergic conjunctivitis because it plays a crucial role in the first rate-limiting step of the inflammatory cascade by hydrolyzing the acyl-ester bond and generating arachidonic acid [1]. Arachidonic acid is then converted to prostaglandins and leukotrienes.

There are two phases of the reaction: an immediate early phase caused by the degranulation of mast cells, leading to the release of histamines, leukotrienes, prostaglandins, chemokines and cytokines; and a late phase that occurs approximately 4–6 h after, as a result of chemotactic factors causing an influx of eosinophils and T lymphocytes.

Developments in seasonal and perennial allergic conjunctivitis

There are numerous chemotactic mediators that have been identified and quantified in allergic conjunctivitis; however, studies continue to look at the sources and causes of eosinophil and T-lymphocyte influx.

For example, Smit and colleagues [2] hypothesized that the epithelial cells of the ocular surface also contribute to the release of inflammatory or chemotactic mediators. They evaluated TNF- α and INF- γ for their effects on the release of two chemotactic mediators: IL-8 and the regulated upon activation, normal T cell expressed and secreted (RANTES) chemokine. Human conjunctival epithelial cells (primary cells or HC0597 cell line) were grown and stimulated with various concentrations of TNF- α , INF- γ , or a combination of both. Supernatants were collected at 6-, 24-, and 48-h intervals and subsequently analyzed by enzyme-linked immunosorbent assay for analysis of IL-8 and RANTES [2]. Their results showed that IL-8 and RANTES were stimulated in a dose-dependent and time-dependent manner after treatment with TNF- α , but INF- γ only induced RANTES release. Those treated with both TNF- α and INF- γ showed a synergistic increase in RANTES release but not IL-8. In conclusion, stimulation of the conjunctival epithelium with TNF- α and INF- γ induced a chemotactic response by IL-8 and RANTES, which could prolong inflammation, possibly by recruiting eosinophils to the ocular surface [2]. This was the first study to compare chemokine release in a specific cell line and primary cell line. The results for chemokine release between each cell line are similar, indicating phenotype similarities [2]. Importantly, this study validated the fact that ocular epithelial cells play a role in the duration of inflammatory response.

In addition to epithelial response, it is also believed that certain pathogens invade the ocular epithelium and elicit allergic responses. Hiroshi Fujishima [3] hypothesized that respiratory syncytial virus (RSV) infects the normal conjunctival epithelium and produces IL-4, causing an allergic reaction. To test this hypothesis Fujishima used several methods, including Giemsa staining, immunocytochemical studies, flow cytometric analysis, and reverse transcriptase polymerase chain reaction (RT-PCR) to examine tear and cytology samples from individuals with allergic and postoperative conjunctivitis. Histamine was assayed by radioimmunoassay, and IL-4 by enzyme-linked immunosorbent assay. Results showed significantly increased levels of IL-4 and histamine in patients with allergic conjunctivitis, while centrifugation of specimens revealed the presence of conjunctival epithelial cells with lymphocytes, mast cells, eosinophils, and higher human leukocyte antigen-DR expression in allergic patients.

RT-PCR revealed increased transcripts of IL-4 and IL-13 in allergic samples. Immunocytochemical study and RT-PCR showed epithelial cell infection with RSV [3]. In summary, it is evident from this study that RSV can and does invade normal ocular epithelial tissue and is associated with a significantly higher IL-4 production than are non-infected cells [3]. RSV invasion therefore begins the inflammatory cascades of allergic conjunctivitis. Clinically, this is important in that topical therapy targeting RSV or IL-4 may reduce or eliminate the synthesis of IgE induced by IL-4, therefore, regulating the production of IgE antibody [3].

Lastly, Sohn *et al.* [1] suggested that transglutaminase inhibitors reverse the inflammation related to allergic conjunctivitis. Their hypothesis is based on previous research showing that PLA2 is activated by transglutaminase 2. Additionally, steroidal antiinflammatory drugs act by inducing proteins that inhibit PLA2. Sohn and colleagues believe, however, that transglutaminase 2 inhibitors may increase the efficacy of inhibiting PLA2 activity. To test their theory, recombinant peptides were constructed containing sequences from pro-elafin for inhibition of transglutaminase 2 and from lipocortin-1, lipocortin-5, and uteroglobin for inhibition of PLA2. In a guinea pig model, the recombinant peptides had a dual inhibitory effect on transglutaminase 2 and PLA2, reversing inflammation caused by ragweed [1]. The use of recombinant peptides potentially plays a role in future treatment, perhaps giving a safer alternative to steroid preparations [1].

Atopic keratoconjunctivitis and vernal keratoconjunctivitis

AKC and VKC are both severe forms of ocular allergy. Although very similar to SAC and PAC in the previously described inflammatory processes, AKC and VKC are often severe, chronic, and can compromise the cornea, causing ulcers, scarring, and can ultimately lead to vision loss. Symptoms of AKC and VKC include itching, ropy mucous discharge, tearing, and photophobia. Conjunctival and corneal vascularization and scarring, along with atopic dermatitis, are characteristics of AKC, while giant papillae of the superior tarsal conjunctiva, Trantas' dots, severe conjunctival hyperemia, and corneal ulceration with scarring are diagnostic of VKC. Because of 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. The following section will explore exactly that.

Developments in atopic and vernal keratoconjunctivitis

An area of interest in allergic keratoconjunctivitis is the role of eosinophils and neutrophils. Although they are known to play a role in the inflammatory processes, this

is not exactly understood. Eosinophils are commonly associated with atopic disease [4•]. This association may be due to the toxic cationic proteins contained within the eosinophil granule. Major basic protein (MBP) is the major constituent of the eosinophil granule and comprises its core, and in high concentrations has been shown to be cytotoxic to tissues.

Likewise, neutrophils have granule proteins, such as neutrophil elastase, which may contribute to the inflammatory process. Stefan Trocme and colleagues [4•] performed a retrospective study to examine the participation of both eosinophils and neutrophils in AKC and VKC. Conjunctival specimens were obtained from patients with AKC and VKC, and from disease-free participants. Indirect immunofluorescent staining was used to localize neutrophil elastase and MBP in serial sections of all specimens. Results showed extracellular deposition of both neutrophil elastase and MBP in patients with AKC and VKC; however, minimal neutrophil elastase and no MBP were found in normal specimens [4•]. Therefore, it is suggested that both neutrophils and eosinophils play an active role in AKC and VKC.

Similarly, a case report by Messmer *et al.* [5] looked at the eosinophil granule proteins and their role in corneal ulceration and scarring of a 76-year-old man with long-standing atopy, asthma, and severe bilateral chronic AKC. Three corneal buttons were examined by light microscopy and by immunofluorescence. MBP as well as eosinophil cationic protein were identified in all three buttons. They were found not only in the area of ulceration but also underneath intact corneal epithelium. Thus, toxic eosinophil proteins may be responsible for corneal instability in patients with AKC [5].

In addition to studying the effects of eosinophils on ocular tissue, questions exist on eosinophil recruitment and activation. Leonardi *et al.* [6] specifically studied eotaxin-1 and eotaxin-2, potent CC chemokines that have been shown to attract and activate eosinophils by acting via the chemokine receptor (CCR)-3 expressed on eosinophils [6]. The methods included taking tear and mucus samples from active VKC and AKC patients, as well as disease free patients. Eotaxin-1 and eotaxin-2 levels were examined in the tears, mucus, and culture medium. Results showed high levels of eotaxin-1 and eotaxin-2 in the mucus of VKC patients, but only eotaxin-2 was significantly increased in the tears. Eotaxin levels significantly correlated with the percentage of eosinophils in tear fluid. The corneal involvement of VKC patients was significantly correlated with eotaxin-1. In conclusion, eotaxins 1 and 2 are thought to play a role in eosinophil recruitment and in the pathology of VKC and AKC [6].

Thinking clinically about the previous study, the CCR-3 for eotaxin leaves open a possible target for treatment. Fukagawa and colleagues [7] aimed to determine the suppressive effects of antibodies against CCR-1 and CCR-3. Cultures of human corneal keratocytes were incubated with IL-4 and TNF- α for 48 h. Tears of severely allergic patients were stained for CCR and were pre-incubated either with or without anti-CCR-1 or anti-CCR-3. The results demonstrated that anti-CCR-1 and anti-CCR-3 both inhibited eosinophil chemotaxis, but that anti-CCR-3 was more effective. Therefore, inhibition of CCR-3 may be a potential target for treatment [7].

Safety and efficacy of topical treatment

Various pharmaceutical preparations are available for the treatment of ocular allergies, including ophthalmic antihistamines, mast cell stabilizers, a combination of both antihistamines and mast cell stabilizers, non-steroidal antiinflammatory drugs, and topical ophthalmic steroids. However, the efficacy and safety of these treatment methods vary. Antihistamines, mast cell stabilizers, and non-steroidal antiinflammatory drugs are most effective in mild to moderate cases of early stage conjunctivitis. These agents have a limited and focused ability to block the inflammatory cascade. Of particular interest are the topical corticosteroids because they have the ability to block, reduce, or inhibit the production of all inflammatory mediators in the cascade. They have been shown to be more effective in treatment of more severe and late stage conjunctivitis, but, unfortunately, have significant side effects, including increased intraocular pressure, cataracts, and increase susceptibility to viral and fungal infections.

Until recently, there were no studies evaluating the long-term safety and efficacy of using loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis [8]. Ilyas and colleagues [8] conducted a retrospective review of 397 patients from three private ophthalmologic practices that were long-term users of loteprednol etabonate 0.2%. Of those 397 participants, 159 had 12 months or greater usage. There were no reports of adverse effects of any of the 159 patients who had continuous use ranging from 120 drops to 3741 drops per eye over the course of treatment. It was concluded that loteprednol etabonate 0.2% ophthalmic solution is safe and effective for treatment of seasonal and perennial allergic conjunctivitis [8].

Additionally, the safety and efficacy of desonide phosphate has been evaluated for the treatment of SAC [9]. Using the conjunctival provocation test model, Leonardi and colleagues found that desonide phosphate pretreatment reduced both the early and late phase reactions. Participants were pretreated with desonide

phosphate and a placebo for 30 min, 6 h, or 48 h prior to conjunctival provocation test. The drug was increasingly effective the longer the pretreatment, with 48 h being highly effective in reducing itching, tearing, and hyperemia [9]. This indicates that pretreatment with a low dose steroid can inhibit or attenuate transition from early acute phase to the late more chronic phase of an inflammatory response. No side effects or adverse reactions were observed. In addition, a seasonal study was also performed comparing desonide and fluorometholone. No statistically significant differences existed among treatments. However, desonide has lower systemic absorption than fluorometholone, making it a comparable, if not a better choice of treatment [9].

Lastly, a double-blind, placebo-controlled trial was performed to evaluate the safety and efficacy of cyclosporine 2% eye drops in the treatment of vernal keratoconjunctivitis [10]. Cyclosporine is an immunosuppressant that blocks helper T-lymphocyte proliferation and IL-2 production, and it inhibits histamine release. It has been used in the past to help prevent graft and organ rejection. However, few controlled trials have been performed using this drug for treatment of VKC and some results have been conflicting [10]. Pucci and colleagues evaluated the efficacy of cyclosporine 2% eye drops in 24 patients with VKC that was non-responsive to other treatments. For the first 2 weeks the study was conducted as a double-blind, placebo-controlled study, but then was followed by an open trial for approximately 4 months. One eye was treated with the cyclosporine drops, while the other was treated with a placebo. Signs and symptoms of ocular allergy were recorded at 2 weeks, 4 weeks, and again at 4 months. At 2 weeks, the eye treated with cyclosporine showed significantly less ocular signs and symptoms ($P < 0.001$) compared with baseline, while the placebo treated eye showed some improvement in signs ($P < 0.001$). At 4 weeks, the scores for the cyclosporine treated eye showed no further improvement, while scores for the placebo were reduced (subjective $P < 0.005$ and objective $P < 0.001$). Similarly, the scores at 4 months showed continued therapeutic effects of cyclosporine. To monitor safety, serum electrolytes, alanine aminotransferase, aspartate aminotransferase, and creatinine were normal for participants at the onset of the trial. No significant variations were noted throughout the treatment. Additionally, blood levels of cyclosporine were always less than the lower

detectable limit of 20 ng/l, and blood pressure was always within normal range. It was concluded that topical cyclosporine 2% was effective and safe in the treatment of VKC. It was suggested that cyclosporine eye drops be considered for VKC in order to prevent complications of both non-treatment and of corticosteroid use [10].

Conclusion

In conclusion, research has made significant headway in unfolding the complexity of ocular allergy. Inflammatory mediators have been identified and quantified, as have various sources of inflammation and pathogens. Based on these research findings, pharmaceuticals have possibilities of new drug targets. However, the safety and efficacy of existing treatments must continue to be tested. Ocular allergies are affecting millions of people worldwide, warranting the wonderful research that is being done to help battle the human body's unwanted inflammatory response.

References and recommended reading

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- of special interest
- of outstanding interest

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