

The Anti-Inflammatory Effects of Therapies for Ocular Allergy

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Abstract

Purpose: In this review, we aim to summarize the currently available compounds targeting the different components of the inflammatory cascade triggered by an ocular allergic reaction, from mast cells to eosinophils and lymphocytes, with a special focus on specific signs and symptoms that are related to them.

Methods: The article gives a review of topical therapies utilized to treat the various forms of allergic conjunctivitis, starting from the first drugs developed in the 1980s up to the new compounds that are currently being developed. These include antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory agents, and topical immunosuppressants.

Results: The treatment options that have been developed for allergic conjunctivitis in the past 30 years are the result of a better understanding of the pathogenic mechanisms involved in the initiation and perpetuation of the ocular allergic reaction, which is guiding us toward a more specific treatment approach.

Conclusions: Several reports and literature reviews have demonstrated that a better knowledge of the immunopathogenesis of the different types of ocular allergy has improved the treatment choice resulting in better clinical outcomes for ocular allergy sufferers. Specifically, the development of novel compounds targeting specific cells and/or cytokines involved in the ocular immune reaction provided safer and more tolerated drugs for both mild-to-moderate and severe forms of allergic conjunctivitis. The correlation of clinical responses to drugs with what we understand about the molecular mechanisms involved could possibly prove useful for developing more standardized treatments in the near future.

Introduction

OCULAR ALLERGY REPRESENTS one of the most common conditions encountered in clinical practice, and the ophthalmologists can count on a wide range of topical and systemic drugs for its treatment.^{1–4} Specifically, the control of ocular allergic reactions is usually targeted with topical eye drops, such as antihistamine drugs, mast cell degranulation inhibitors/mast cell stabilizers, anti-inflammatory compounds (both nonsteroidal and corticosteroids), and, more recently, multiple action compounds and novel immunosuppressive agents, such as cyclosporine and tacrolimus.^{5–9} Furthermore, basic and clinical research have provided in the past years a better understanding of the cells, mediators, and immunologic events that are involved in the ocular allergic reaction, resulting in the development of new pharmacological agents, including more potent mast cell stabilizers and low-dose corticosteroids, which have improved the

efficacy and safety of ocular allergy treatment.^{10–18} However, despite the wide range of agents available, ocular allergy is still a challenge to ophthalmologists, in particular, for the more severe cases with corneal involvement and sight loss that need a more aggressive approach.^{19–21}

According to their pathogenesis and clinical picture, ocular allergies are classified into clinically mild forms, such as seasonal and perennial allergic conjunctivitis (SAC and PAC) as well as giant papillary conjunctivitis, and chronic potentially blinding forms, such as atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) that do not spare the cornea.^{22–27} The presence of conjunctival papillae or follicles, the type of conjunctival secretion, the involvement of the cornea, and the prevalence of specific symptoms, including itching, redness, burning, photophobia, tearing, or dryness, may help in the differential diagnosis between these forms of ocular allergy, which is often difficult due to their similarities.^{28,29} In fact, despite the clinical, immunologic,

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prognostic, and therapeutic differences of these clinical entities, all the different forms of ocular allergy may share a common allergen sensitization, similar symptoms, but a variable response to topical anti-allergic, anti-inflammatory, or immunosuppressive agents.^{2,5-9,18,30}

To overcome the long-term complications caused by such a variable response to more classical anti-allergic treatment, new generation therapeutics act on the entire inflammatory process or try to modulate the allergic reaction early by specific inhibition of crucial components of the allergic cascade.^{31,32}

The efficacy of topical anti-allergic compounds has been extensively studied in the past 45 years, especially after the launch of the first anti-allergic eye drops, cromolyn, in the 1980s.^{8,9,20} Several classes of novel ophthalmic anti-allergic medications have then been developed to inhibit the specific mechanism of the allergic inflammatory cascade and to treat clinical signs and symptoms of allergic conjunctivitis.^{16,31} The last in the chronological order are the so-called multiple action drugs, such as azelastine, epinastine, ketotifen, and olopatadine, which have recently been developed to combine the antihistaminic effect, the mast cell stabilization effect, and the anti-inflammatory effect, acting on several immune cells. This pharmaceutical class is, therefore, quickly becoming the first choice for the prevention and treatment of allergic conjunctivitis sufferers. In fact, acting as antihistaminic drugs, they antagonize histamine receptor binding, providing immediate relief of early-phase symptoms; acting as mast cell stabilizers, they inhibit their degranulation; and acting on the immune cells of the late-phase reaction, they also reduce ocular surface damage in both the early and long term.³² Moreover, several studies are currently ongoing for the identification of novel targets of allergy treatment, including treatments capable of shifting the immune reaction (such as probiotic eye drops).

Despite the recent development of multiple action compounds and these novel possibilities, each compound exerts a different effect on the allergic reaction and, therefore, all anti-allergic drugs—from older to newer experimental treatments—remain today as valid therapeutic options for ocular allergy sufferers.⁶⁻⁹

In this review, we aim to summarize and briefly describe all the available compounds targeting the different components of the ocular allergic reaction, from mast cells to eosinophils and lymphocytes, with a special focus on specific signs and symptoms that are related to them. The article gives a review of currently available topical drugs and includes therapeutic compounds utilized to treat the various forms of allergic conjunctivitis, starting from the first compounds developed in the 1980s up to the new treatments that are being developed in *in vitro* and *in vivo* studies on animal models. Future developments in the manipulation of eosinophilic products, cytokines, and adhesion molecules may also prove relevant in arresting the allergic reaction by targeting different components that are specific for each kind of ocular allergic disease.

Cellular and Molecular Responses in Allergic Conjunctivitis

The various therapeutic options for the different forms of allergic conjunctivitis are selected based on the current understanding of which cellular responses are involved. Each

clinically distinct form of noninfectious conjunctivitis involves different combinations of cell and molecular interactions. Therefore, before moving to an overview of the currently available treatment options for the different types of ocular allergy, a brief summary of their specific pathogenic mechanisms is reported below.

Seasonal allergic conjunctivitis

The predominating immune response occurring in SAC is an immediate (type 1) hypersensitivity response where conjunctival mast cells and their secreted products primarily orchestrate the inflammatory response. On exposure to allergen (pollens), mast cells degranulate, releasing histamine, leukotrienes, proteases, and other preformed mediators, including platelet-activating factor and cytokines. On binding to its receptors (H1 and H2), histamine induces vascular leakage, resulting in further cellular infiltration of eosinophils and neutrophils from the blood, leading to chemosis. Although some neutrophils and eosinophils have been found in less than half of symptomatic patients with SAC, little or no T-cell infiltration was observed.¹⁰

Perennial allergic conjunctivitis

The inflammatory response in PAC also involves mast cells, although due to the continued presence of the allergen, usually house dust mite or cat dander, there is a more chronic activation of mast cells.²² Hence, neutrophils and some T cells have also been detected in the conjunctival tissues, probably resulting from the release of chemokines, which attract these cells to the site of inflammation during the persistent allergen-driven inflammatory response.

Vernal keratoconjunctivitis

During VKC, studies have identified cells of both innate and adaptive immunity becoming activated with eosinophils predominating and CD4⁺T lymphocytes, as well as mast cells and neutrophils infiltrating the conjunctival sub-epithelial and stromal tissues.¹⁸ These cell types are able to secrete a wide range of proinflammatory cytokines [interleukin (IL)-3, IL-4, IL-5, IL-6, transforming growth factor alpha, tumor necrosis factor alpha, chemokines (IL-8, RANTES) and multiple mediators (granule proteins: eosinophil cationic protein, major basic protein, and eosinophil-derived cationic protein) to amplify the inflammatory response. It has been found that the degree of eosinophil activation (expressing ICAM-1 or HLA-DR) correlates more with disease severity than the total numbers of eosinophils.³³ There is also evidence of upregulation of adhesion molecules and HLA-DR on conjunctival fibroblasts and conjunctival epithelial cells, suggesting the activation of these cells.^{34,35}

Atopic keratoconjunctivitis

In AKC, the predominant cell types infiltrating the conjunctival tissues are CD4⁺T cells, eosinophils, and neutrophils.²⁷ In contrast to VKC, the T-cell cytokine profile is more Th1-like since interferon- γ expression was upregulated in AKC T cells.³⁶ Similar to VKC, there are alterations to the conjunctival epithelium and evidence of tissue remodeling and collagen deposition, reflecting the chronic immune-mediated disease.

There are differences between VKC and AKC in the patterns of cytokines colocalizing to conjunctival eosinophils, with those in VKC mainly expressing IL-3, IL-5, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF), whereas in AKC, eosinophils express mainly IL-4, IL-8, and GM-CSF.³³ Therefore, although the specific cellular interactions are currently unclear, the differences in cellular and cytokine profiles suggest that different disease mechanisms are involved in each form of ocular allergy.

Treatment Options

As mentioned above, several therapeutic options are available for the different forms of allergic conjunctivitis and may be used to treat most of them since they all share common pathogenic mechanism (Table 1). Nevertheless, selecting the most appropriate treatment based on the understanding of which cellular responses are involved in the different forms of ocular allergy could result in better management and long-term results. A brief summary of different classes of topical anti-allergic compounds is reported below.

Antihistamine/mast cell stabilizers

Levocabastine. Levocabastine is an H1-receptor antagonist and one of the first antihistamine compounds used to treat patients with allergic conjunctivitis.³⁷ Although it has been already available for many years, it is still widely used today as one of the most successful treatments for mild-to-moderate ocular allergy sufferers. In fact, levocabastine is well known to significantly decrease ocular itching, eyelid swell-

ing, chemosis, conjunctival hyperemia, and to improve the patients' quality of life.³⁸ It is also associated with an excellent compliance to therapy for patients, as it remains one of the most tolerated anti-allergic therapies currently available in the market.

Epinastine. Epinastine is a topically active direct H1 receptor antagonist that has affinity for the H2 receptor. Since it also inhibits the release of histamine and other mediators from mast cells, it can also be classified as a multiple action compound.³² Its action lasts at least 8 h, and it should be administered twice daily. It can be used safely in children (recommended after 3 years of age). Due to its immediate anti-allergic effects, it is indicated for the prevention of itching associated with allergic conjunctivitis and for the treatment of eyelid swelling and conjunctival chemosis. It has also been proven effective in reducing conjunctival, episcleral, and ciliary hyperemia following specific allergen challenge in a randomized, double-masked vehicle-controlled study performed on 67 patients with allergic conjunctivitis.³⁹

Pheniramine maleate. As the above, pheniramine is an antihistamine compound that has been proven effective in reducing ocular allergy symptoms.⁴⁰ It is widely used systemically to treat both eye fever and urticaria. In contrast to levocabastine, it has a relatively strong sedative effect, which makes it a drug that is often used off-label as a sleeping aid by allergic patients.⁴¹

Obviously, these effects are not significant for the eye drop formulation that is characterized by a minimal systemic

TABLE 1. MEDICAL TREATMENTS FOR ALLERGIC CONJUNCTIVITIS

Class	Drug	SAC/PAC	VKC	AKC	Target
Antihistamine and mast cell stabilizers	Levocabastine, pheniramine, pemirolast, lodoxamide	First choice	Maintenance treatment, prevention of reactivations	Maintenance treatment, prevention of reactivations	Compete with H1 receptors, inhibit histamine release
Corticosteroids	Loteprednol, ^a dexamethasone, fluorometholone, ^a prednisone, rimexolone ^a	Avoid if possible	Preferably only as a "burst" treatment during disease reactivations	Preferably only as a "burst" treatment during disease reactivations	Immune reaction
Immunosuppressant	CsA, tacrolimus	Usually not necessary	Steroid-sparing for chronic use	Steroid-sparing for chronic use	Immune reaction, inhibit IL2 activation on lymphocytes
NSAIDs	Ketorolac	May be used to avoid steroid use	May be used to reduce steroid use	May be used to reduce steroid use	Inflammatory cascade, reduces PGE2
Multiple action compounds	Azelastine, nedocromil, emedastine, epinastine, ketotifen, olopatadine	Prevention and treatment of acute phase	Prevention and treatment of reactivations	Prevention and treatment of reactivations	Compete with H1 (and/or H2) receptors, inhibit histamine release, inhibit cytokine production, reduce eosinophil chemotaxis

^aReduced long-term side effects such as cataract formation and glaucoma.

SAC/PAC, seasonal and perennial allergic conjunctivitis; AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis; NSAIDs, nonsteroidal anti-inflammatory drugs.

uptake that can also be reduced by pressing onto the lacrimal puncta during instillation.

Pemirolast. Pemirolast is a mast cell stabilizer that also features antihistamine properties. It is used mainly for the prevention of itching associated with allergic conjunctivitis of different kinds. In fact, in different studies on SAC patients, it has been proven to significantly decrease itching and, to a lesser extent, redness. It also been proven to decrease ocular itching after conjunctival allergen challenge.⁴²

Lodoxamide tromethamine 0.1%. Lodoxamide tromethamine 0.1% is an effective mast cell stabilizer that prevents the release of histamine and leukotrienes.⁴³

The mediator release from mast cells is thought to be inhibited by lodoxamide through the inhibition of calcium influx in the cell, thereby indirectly inhibiting increased vascular permeability. Compared to the older mast cell stabilizer, cromolyn, it is as much as 2,500 more potent in inhibiting mediator release from mast cells. Unfortunately, this cellular effect is not paralleled by a stronger clinical efficacy: in fact, lodoxamide appears to be roughly equivalent to cromolyn in controlling the symptoms of SAC and PAC, as well as more severe forms, such as VKC.^{44,45}

Olopatadine. Olopatadine is another anti-allergic compound that inhibits mast cell degranulation. Since it also antagonizes the H1 histamine receptor, it can also be considered a multiple action compound.³²

Olopatadine is used successfully to manage itching, redness, chemosis, tearing, and lid swelling during the ocular allergic reaction. To support the mast cell stabilizing ability of olopatadine that has been widely demonstrated in *in vitro* and *in vivo* studies, several clinical trials have shown that it significantly reduces itching and redness with an immediate effect that lasts as long as 8 h after treatment.⁴⁶

Although the olopatadine has been already available for several years, novel formulations have recently been developed and approved for once-a-day administration, which should significantly increase patients' compliance to therapy.

Immunosuppressive compounds

Corticosteroids. Corticosteroids may be extremely effective in relieving symptoms of allergic conjunctivitis, but due to the chronic recurrent nature of the disease, which in the vast majority of cases is a benign condition without long-term complications, these drugs should be used with extreme caution and preferably only as a "burst" treatment for no more than 1–2 weeks. In fact, the ophthalmic use of topical steroids is associated with severe complications that may lead to sight loss, including glaucoma, cataract formation, and infections of the cornea and conjunctiva. Any prolonged use should therefore be carefully considered, and the patient should be advised of the possible detrimental long-term effects and strictly monitored by an ophthalmologist.⁴⁷

There are several topical corticosteroids currently available. Fluorometholone 0.1% eye drops are often selected as a useful treatment of external ocular inflammation and are highly effective in allergic conjunctivitis.⁴⁸

Compared to other corticosteroids, fluorometholone is also relatively safe as it appears to penetrate the cornea well

but is inactivated quickly in the anterior chamber. Therefore, it is believed that fluorometholone is inactivated before it has an opportunity to combine with trabecular meshwork or lens receptors, reducing the risk of glaucoma and cataract formation compared with more potent corticosteroids, such as prednisolone and dexamethasone.⁴⁹

To overcome the obstacles of these stronger corticosteroids, two compounds that have recently been investigated for ophthalmic use show substantial promises in the treatment of ocular allergy: rimexolone and loteprednol etabonate.⁵⁰

Rimexolone is a derivative of prednisolone, but it is quickly inactivated in the anterior chamber, resulting in only slightly higher risks of complications than fluorometholone.⁵¹

Loteprednol etabonate also seems to be rarely associated with a significant rise in intraocular pressure.⁵² Due to its highly effective anti-allergic action, a low-dose loteprednol etabonate has been approved for the relief of allergic conjunctivitis.⁵³

Cyclosporine A. Cyclosporine is a fungal antimetabolite that can be used as an anti-inflammatory drug due to its ability to inhibit IL-2-mediated activation of lymphocytes. It is most often used systemically to prevent the rejection of various solid tissue transplants, but it has also been used as an eye drop formulation in a variety of conditions, including dry eye, VKC, and in high-risk corneal transplant patients.⁵⁴

The use of cyclosporine in allergic conjunctivitis appears to reduce significantly the number of recurrences of the disease during the year.⁵⁵

Cyclosporine appears to interfere with antigen processing and presentation of antigen to the uncommitted T lymphocytes, suggesting that it could be more promising to treat the chronic rather than the acute aspects of an allergic conjunctivitis.

Tacrolimus. Tacrolimus is a novel promising immunomodulating medication currently under evaluation in ongoing clinical trials. However, most of its prospective future applications being evaluated are related to uveitis rather than ocular allergy.^{56,57}

Similar to cyclosporine, the efficacy of tacrolimus may be limited by the fact that it needs a few weeks to achieve a maximum effect. Therefore, its use may be limited to chronic rather than acute allergic reactions.

Multiple action compounds

Several clinical trials have been performed to demonstrate the safety and efficacy of multiple action drugs in improving the signs and symptoms of allergic conjunctivitis. Among them, the following are the most commonly used in ophthalmology practice today:

Azelastine. Azelastine is a phthalazinone derivative that has been approved for the prevention or treatment of itching due to allergic conjunctivitis.^{31,58} It is considered a multiple action compound because it inhibits histamine release from allergen-stimulated mast cells, it suppresses the inflammatory cascade, and it has also been proven to decrease the expression of ICAM-1, to reduce eosinophil chemotaxis, and to inhibit platelet-activating factor.^{59,60} Finally, it also

interferes with calcium influx in mast cells and inhibits the binding of histamine to its H1 histamine receptor.^{61–64}

In clinical practice, these effects result in a significant reduction of itching, and, to a lesser extent, of redness in both SAC and PAC.

Nedocromil. This disodium salt of pyranoquinolone dicarboxylic acid is approved for the treatment of itching associated with allergic conjunctivitis. It is considered a multiple action drug as it acts as a mast cell stabilizer by inhibiting the degranulation of mast cells, it prevents the release of histamine and tryptase, hence preventing the synthesis of prostaglandins (PGs) and leukotrienes, it decreases neutrophil and eosinophil chemotaxis and renders them unresponsive to mediators, it blocks the expression of cell surface adhesion molecules involved in eosinophil chemotaxis, and it decreases vascular permeability induced by inflammation.

Its main effect is a rapid reduction of itching and, to a lesser extent, of redness associated with different forms of allergic conjunctivitis. It has an onset of action 2 min after dosing and a duration of about 8 h.^{65–67}

Emedastine. Emedastine is another multiple action compound that has been proven more effective than nedocromil in alleviating redness and itching at 3 and 10 min after allergen challenge.⁶⁸ Moreover, in a double-blind randomized study involving 222 patients, emedastine eye drops were more effective than levocabastine eye drops in the prevention and treatment of the signs and symptoms of allergic conjunctivitis in both adults and children.^{69,69–71}

In vivo studies suggest that the antipruritic effects of emedastine derive from a blockade of the leukotriene B4 action.⁷²

Ketotifen. Ketotifen is a benzocycloheptathiopen derivative approved for the temporary prevention of itching due to allergic conjunctivitis. It has been used for several years as an anti-allergic drug for the management of bronchial asthma, atopic dermatitis, seasonal or perennial rhinitis, allergic conjunctivitis, acute or chronic urticaria, and food allergy.⁷³ It is a selective noncompetitive blocker of the H1 histamine receptor. However, it can be considered a multiple action compound as it also inhibits the inflammatory allergic conjunctivitis mediator release from mast cells, basophils, and eosinophils.⁷⁴ It inhibits chemotaxis and degranulation of eosinophils, type 1 hypersensitivity reactions, and leukotriene activity. It is also an inhibitor of platelet-activating factors.⁷⁵

As with the other multiple action compounds previously examined, ketotifen appears to be more effective in reducing itching than the conjunctival hyperemia associated with allergy.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been proposed as an alternative to the long-term corticosteroid use, which, as is well known, carries important side effects, such as cataract formation and glaucoma. NSAIDs are available for ocular allergy treatment as eye drop formulations alone or together with vasoconstrictors, such as naphazoline.

Ketorolac tromethamine. Although it may be associated with mild transient burning upon instillation, this NSAID is sometimes used to relieve symptoms associated with the inflammatory cascade triggered at the ocular surface by allergic conjunctivitis. It is known to reduce the levels of PGE2 in tears, which may explain the effect of ketorolac in relieving itching: in fact, research by Woodward et al.⁷⁶ suggests that some of the PGs, particularly PGE2 and PGI2, may be pruritogenic.

Discussion

In this study, we reviewed treatment options that have been developed for allergic conjunctivitis in the past 30 years. These developments, observed over time, have allowed us to better understand the pathogenic mechanisms involved in the initiation and perpetuation of the ocular allergic reaction, guiding us toward a more specific treatment approach. In addition, the correlation of clinical responses to drugs with what we understand about the molecular mechanisms involved could possibly prove useful for developing more standardized treatments in the near future, thus identifying new treatment targets.

Several reports and literature reviews have widely demonstrated that better knowledge of the immunopathogenesis of the different types of ocular allergy has improved the treatment choice resulting in better clinical outcomes for ocular allergy sufferers. Specifically, the development of novel compounds targeting specific cells and/or cytokines involved in the ocular immune reaction has led to the availability for ophthalmologists of safe drugs for both mild-to-moderate and severe forms of allergic conjunctivitis. These include antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory agents, and topical corticosteroids, such as new generation steroids with reduced side effects (i.e., loteprednol etabonate).

Nevertheless, since a drug's safety is at least as important as its efficacy, the long-term safety of all anti-allergic treatments must always be considered during the decision-making process of treatment despite the wide range of available options. In fact, only a combined evaluation of safety and efficacy of a therapeutic intervention may allow a balanced risk/benefit ratio for evidence-based recommendations. In this perspective, it must be remembered that, although the treatment options for ocular allergy sufferers have considerably increased over the past 3 decades, corticosteroids remain one of the most effective treatments in terms of immediate clinical success. However, their use must not be chosen as a shortcut to patient satisfaction, especially for those affected by more severe chronic ocular allergic diseases since even new generation topical corticosteroids carry important side effects, such as cataract formation and glaucoma.

Author Disclosure Statement

No competing financial interests exist.

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