

Ocular Allergy Treatment

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Nonpharmacologic interventions are commonly used as first-line treatment of ocular allergy and include avoidance, cold compresses, lubrication, and the use of disposable daily contact lenses. Pharmacologic management of ocular allergy has increased exponentially over the past decade.

Clinically available agents are being expanded to specifically address the various signs and symptoms of inflammation associated with ocular allergy. The increased focus on drug development for treating ocular allergy correlates with the increased awareness of its prevalence in the industrialized countries of the United States and in the European Union. Increasing recognition of the prevalence of ocular allergy has also resulted in an upsurge of research into the pathophysiology and immunology defining the various forms of inflammation and identifying the specific roles of the various mediators of inflammation. This focus has become the basis for the development of novel pharmacologic targets for treating the ocular allergy inflammatory cascade, which include those that target the mast cells, the IgE antibody, and the release of early and late phase mediators (eg, histamine, prostaglandins, leukotrienes, cytokines). The search for more effective medications for ocular allergy required the development of a standardized model, such as the conjunctival allergen challenge (CAC), also known as the *conjunctival provocation test*. This model allowed more efficient assessment of the efficacy of new agents in treating the allergy signs and symptoms of erythema (redness), pruritus (itching), epiphora (tearing), lid swelling, and conjunctival swelling (chemosis). Many newer agents that have been tested in this model for their impact on the subjective and objective signs have also started to measure the objective efficacy through the presence of cytologic biomarkers, further advancing the understanding of the conjunctival-associated lymphoid tissue allergic response (Fig. 1).

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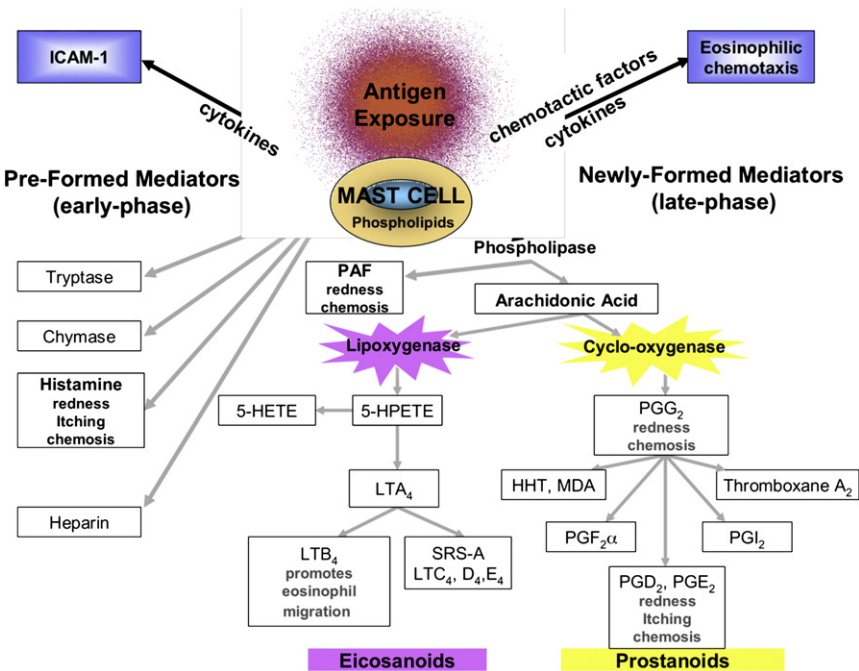


Fig. 1. Effects of the inflammatory cascade in treating allergic conjunctivitis: central role of the mast cell. Antihistamines induce rapid relief from H₁-receptor-mediated itching and inhibit redness through H₂-receptor blockade; mast cell stabilizers stabilize the mast cell membrane, blocking the release of histamine, cytokines, and chemotactic factors; nonsteroidal anti-inflammatory drugs block cyclooxygenase, preventing release of prostanoids; multiple-action agents (antihistamines and mast cell stabilizers) block histamine activity and release, expression of chemokines and intercellular adhesion molecule-1, and leukocyte infiltration; and corticosteroids block all mediators through phospholipase inhibition, increased synthesis of histidine decarboxylase, decreased synthesis of histaminase, and cell membrane stabilization. HETE, hydroxyeicosatetraenoic acid; HHT, heptadecatrienoic; HPETE, hydroperoxyeicosatetraenoic acid; ICAM-1, intercellular adhesion molecule-1; LT, leukotriene; MDA, malonyldialdehyde; PAF, platelet activating factor; PG, prostaglandin; SRS-A, slow reacting substance of anaphylaxis.

Historically, multiple agents have been used to manage allergic conjunctivitis. The classes of agents have included vasoconstrictors, oral and topical antihistamines, mast cell stabilizers, multiple-action agents, nonsteroidal anti-inflammatory agents (NSAIDs), and corticosteroids. Vasoconstrictors are widely available as over-the-counter agents but are not recommended because they are nonspecific and not pharmacologically active in the cascade of events that leads to the overall allergic biphasic reaction. Although they have a rapid onset of action, their reduction of redness is short-lived because of tolerance and they cause rebound hyperemia (ie, the development of conjunctivitis medicamentosa).

Oral antihistamines interfere with systemic allergic events that involve the eye but were clearly inferior compared with topical antihistamines, showing slower onset [1]. Oral antihistamines have as much as a 1- to 2-hour delay from systemic antihistamine administration to delivery to ocular tissues through the tears, whereas topical application provides immediate relief. In addition, oral antihistamines have also been associated with excessive drying, leading to more clinical problems with tear film dysfunction in many patients.

Overall, mast cell stabilizers have a slower onset of action than antihistamines, require multiple daily applications to truly achieve mast cell membrane stabilization, and require initiation before mast cell activation to prevent the initial trigger of the allergic cascade. They have been most useful in seasonal management of chronic ocular allergy disorders, such as vernal keratoconjunctivitis (VKC) and chronic giant papillary conjunctivitis, and have been shown to improve healing time of corneal involvement.

The newer multiple-action agents that were previously referred to as *dual-action agents* (ie, having histamine blocking and mast cell stabilizing effects) have been the cornerstone of treatment because they incorporate multiple actions, including binding to H₁ and H₂ receptors, mast cell stabilization, and down-regulation of various inflammatory markers, including eosinophils, neutrophils, adhesion molecules, interleukins, and other cytokines that impact the early and late phases of the conjunctival allergic response. Thus, some of these agents are also approved for prophylactic (ie, prevention) treatment of seasonal allergy conjunctivitis (SAC) in countries other than the United States, and for its acute and long-term treatment of this condition.

NSAIDs specifically inhibit prostaglandins and leukotrienes, theoretically impacting mucus secretion, cellular infiltration, erythema, and chemosis. However, they have only been approved for affecting pruritus and do so weakly compared with the new multiple-action agents. Corticosteroids still remain a cornerstone of treatment for severe and chronic ocular allergy because they exert their anti-inflammatory effects at multiple levels, such as stabilizing intracellular and extracellular membranes; down-regulating inflammation through increasing synthesis of anti-inflammatory lipocortins that block phospholipase A2; inhibiting histamine synthesis in mast cells through blocking histidine decarboxylase; increasing histaminase enzyme and thereby reducing levels of unbound histamine; and modulating transcription factors within mast cell nucleus leading to decreased production of multiple late-phase mediators, which perpetuate the persistent and chronic forms of ocular allergy. However, topical corticosteroids have the potential to induce serious side effects, such as cataracts, elevated intraocular pressure (IOP), and infection, and therefore are best used over short periods (up to 2 weeks). For use beyond 2 weeks, IOP and lens clarity should be monitored with an ophthalmologist or other eye care specialist.

Allergen desensitization involves desensitizing a patient against a specific allergen and is most useful in the management of atopic disorders, including SAC, perennial allergic conjunctivitis (PAC), allergic rhinitis, and certain

forms of asthma. Allergen desensitization is not indicated for VKC or atopic keratoconjunctivitis (AKC). Although highly effective in selected patients who have SAC and PAC, allergen desensitization should be carefully monitored for its overall risk-to-benefit ratio by specialists highly experienced in allergen immunotherapy who have facilities for treating anaphylaxis. Topical immunosuppressive agents, such as cyclosporine A, are alternative therapies for VKC and AKC. Topical cyclosporine A is an immunomodulator that is approved by the U.S. Food and Drug Administration (FDA) for dry eye but not allergic conjunctivitis.

Comparative clinical trials, which include known therapies and placebos, are essential in constructing a solid basis from which to launch any new drug. This approach especially applies to eye drops for treating SAC, for which the symptomatology, already dependent on the vagaries of the natural pollen challenge season, is further influenced by a positive washing action of the placebo eye drops [2]. Prophylactic treatment can be achieved in various models with a variety of agents, especially those considered mast cell-stabilizing or those having multiple actions, such as antihistamines with antieosinophilic or mast cell-stabilizing properties.

The availability of newer mildly sedating and nonsedating second-generation oral antihistamines has provided patients with a myriad of options, especially for ocular allergy treatment. Many of the selective H₁-receptor antagonists have also shown some anti-inflammatory activity that provides additional impact on the ocular late-phase reaction. Topically applied agents still provide faster relief of ocular symptoms compared with oral (within hours) or intranasal agents (within days). Although their duration of action may not be as long as oral systemic agents, health care providers should be aware of the anticholinergic effects of all first- and second-generation antihistamines, because these may exacerbate a concomitant dry eye condition in a patient who has allergies.

Treatment of ocular allergies is largely based on how much these allergies interfere with patient quality of life [3] (ie, severity of symptoms) [4]. Improvement of these quality of life parameters has been shown to take up to 2.5 weeks under treatment. The easiest and most direct therapeutic method is applying a topical agent to the affected tissue. Several topical agents are available for treatment and, to some degree, prophylaxis of ocular allergies, including vasoconstrictors, antihistamines, mast cell stabilizers, and anti-inflammatory agents. Efficacy of these agents varies among patients, and choice of agent depends on the underlying health of the eye and other variables, such as drug cost, contact lens wear, and potential for compliance.

Allergic conjunctivitis is commonly managed with different topical ocular agents. Tools for assessing the efficacy and effectiveness of these agents often includes the conjunctival provocation test or “a day in the park” models.

In addition, more chronic and severe forms of ocular allergy may require a multidisciplinary approach in consultation with an ophthalmologist. Recommendations for ophthalmologic consultation include persistence use of oral or topical steroids, ocular pain, or persistent “red eye.”

Ocular allergy treatment algorithm

The treatment of ocular allergic disorders may follow a stepwise approach based on severity and chronicity that ranges from mildly intermittent to severe persistent forms of conjunctival inflammation. The development of effective therapeutic agents for ocular inflammation was largely ignored until the early 1990s (see Fig. 1). Current treatment is primarily aimed at restoring patient quality of life and may require at least 2 weeks of therapy. Nonpharmacologic therapy consists of minimizing contact with environmental allergens or avoidance, applying cool compresses to the eye, wearing contact lenses, and using preservative-free lubricants [5,6].

Advisory nonprescription interventions

Environmental control

Avoiding allergens remains the first step in managing any ocular disorder; this primary involves using environmental interventions, from removing the offending allergen source to changing occupational venue.

Cold compresses

Cold compresses provide considerable symptomatic relief, especially from ocular pruritus. In general, all refrigerated ocular medications provide additional subjective relief when applied immediately.

Lubrication

Tear substitutes consisting of saline combined with a wetting and viscosity agent, such as methylcellulose or polyvinyl alcohol (“artificial tears”), can be applied topically 2 to 6 times a day as necessary. This substance primarily helps directly remove and dilute allergens that may come in contact with the ocular surface. If tear substitutes are inadequate, ointments or time-released tear replacements (eg, Lacriserts) are commonly used at night to provide moisture to the ocular surface during sleep. The primary concern with chronic lubrication is possible development of a sensitivity to the preservatives found in the multiple-dose bottles. Therefore, patients who require frequent dosing may benefit from use of a preservative-free product to avoid toxic or allergic reactions to preservatives. Unit-dose packaging is generally preservative-free but has increased cost of use. One multidose bottled product, GenTeal (available as a drop or gel), is preserved with sodium perborate, which is chemically converted to water and oxygen within 1 minute of contact with catalase contained in tear film. Rapid degeneration of the preservative allegedly reduces the risk for preservative toxicity or allergy. Ocular lubricants also vary by class, osmolality, and electrolyte composition. No product has emerged as a clear favorite.

Patients should be offered one or two brands from each class of lubricant to try until a suitable product or combination of products is found. A newer form of lubricant, Systane, which contains polyethylene glycol 400 and propylene glycol demulcents with hydroxypropyl-guar as a gelling agent, has been shown to be more effective at reducing the signs and symptoms of dry eye compared with carboxymethylcellulose-containing lubricants [7].

Although the primary pharmacotherapeutic intervention recommended to patients who use specific medication or prescriptions may be to use contact lenses as a “band-aid,” the overall goal of medication is to intervene in the various inflammatory mediators leading to ocular allergy symptoms.

Contact lenses

Overall patients who have seasonal allergy are commonly recommended to avoid contact lens use during seasonal flare-ups. The need for clean lenses with minimal deposit buildup must be stressed, and the use of daily-wear lenses with rigid disinfecting and cleaning techniques is recommended. Alternatively, daily disposable lenses should be used [8]. However, when these individuals wear contact lenses, they have an increased risk for developing ocular infection. The risk is greatest if the lenses are soft and therefore provide for little tear exchange beneath their surface. Under these circumstances, limited tear flow allows for a greater buildup of lens deposits and metabolic wastes, while permitting increased tear evaporation from the lens surface [9].

A primary treatment of any inflammatory response is the use of a mechanical barrier, such as a bandage. This method is commonly used to treat corneal abrasions, with a bandage covering the eye, allowing the eyelid to act as a bandage to promote faster healing of the damaged cornea. In a study evaluating the impact of daily disposable lenses versus standard chronic wear lenses, 67% of patients reported that the 1-day disposable lenses provided improved comfort compared with 18% who preferred a new pair of habitual lenses, suggesting that the use of 1-day disposable lenses may be an effective strategy for managing patients who have allergies who wear contact lenses [10]. Overall, the newer soft silicone with increased gas permeability provides greater comfort (56%) than rigid gas-permeable lens (14%), whereas 63% of nonatopic and only 47% of atopic subjects described their lenses as very comfortable to wear [11,12].

Decongestants

Topical decongestants primarily act as vasoconstrictors, which are highly effective in reducing erythema and are widely used in combination with topical antihistamines [13]. Topical decongestants are applied two to four times a day as necessary. Few studies have compared the commercially available ocular decongestants. Oxymetazoline (Ocuclear) is believed to have a faster onset of action, longer duration of action, and better decongestant effect

than naphazoline (Vasocon) and tetrahydrozoline (Visine). Oxymetazoline 0.025% solution has been shown in earlier studies to significantly improve the symptoms of allergic conjunctivitis when given twice a day [14]. Vasoconstrictors that are commonly used in combination with topical antihistamines are either phenylephrine or naphazoline. All ocular medications containing naphazoline in combination with an antihistamine, except Vasocon-A, have been removed from clinical use because of an evaluation by the FDA in 1992 [15]. Vasocon-A, an antihistamine/decongestant combination, has been proven to effectively treat the signs and symptoms (itch and redness) of allergic conjunctivitis. Visine-A (formerly Ocuhist; Pfizer) contains pheniramine maleate 0.3% and naphazoline 0.025%. The usual dose is one to two drops per eye every 2 hours, up to four times a day. The primary contraindication is for narrow-angle glaucoma. One of the earliest studies comparing the relative efficacies of combination vasoconstrictors in the treatment of allergic conjunctivitis used naphazoline hydrochloride as the vasoconstrictor and antazoline phosphate or pheniramine maleate as the antihistamine in varying concentrations. Patients were specifically queried about their ocular signs (lid swelling, bulbar conjunctival inflammation, and palpebral conjunctival inflammation) and symptoms (itching, tearing, and discomfort) over the course of 1 week. The compounds resulted in different levels of patient comfort and acceptability but were comparable in ameliorating the signs and symptoms [16].

Vasoconstrictors, such as phenylephrine and tetrahydrozoline, are sympathomimetic agents that decrease vascular congestion and eyelid edema through α -receptor stimulation; they do not diminish allergic response. An early study in normal volunteers ($n = 11$) evaluated two commercial preparations of topical ophthalmic vasoconstrictors (0.02% naphazoline HCl and 0.05% tetrahydrozoline HCl) for whitening ability, duration of action, tolerance, and rebound vasodilation. Both significantly reduced baseline redness after a single use (naphazoline > tetrahydrozoline), but naphazoline maintained its whitening ability without tachyphylaxis after 10 days [17]. Although no evidence of “rebound” was reported after 10 days, conjunctivitis from the use of nonprescription (over-the-counter) decongestants that include naphazoline, tetrahydrozoline, or phenylephrine is well-known. In a study of these over-the-counter preparations ($N = 70$; 137 eyes), three clinical patterns of conjunctivitis were reported: conjunctival hyperemia ($n = 50$), follicular conjunctivitis ($n = 17$), and eczematoid blepharoconjunctivitis ($n = 3$). Decongestants were used daily for a median of 3 years (range, 8 hours to 20 years) before presentation and then simply halted. The median time to resolution of symptoms and signs was 4 weeks (range, 1–24 weeks), and patients remained asymptomatic for a median follow-up of 6 months (range, 0–12 years) [18]. Most cases were associated with conjunctival hyperemia, which was similar to the effect of chronic decongestant use on the nasal mucosa (rhinitis medicamentosa) and thus was designated in a case report as *conjunctivitis medicamentosa* [19].

The follicular and eczematoid forms of decongestant-induced conjunctivitis seem to show a T-cell hyperresponsiveness that has been reported with phenylephrine [20]. Although the chronic use of decongestants is associated with conjunctivitis, some experts believe that chronic use of these agents can produce dry-eye symptoms in some patients, which interfere with tear-film adequacy through decreasing mucin-secreting goblet cells. An animal model chronically treated with vasoconstrictors or artificial tears for varying periods showed no significant difference in the number of goblet cells per light microscopic field compared with controls [21].

Antihistamines

Initially, oral antihistamines were used extensively to systemically control the symptoms of allergic rhinitis, which also included allergic conjunctivitis, but with an obvious delayed onset of action on the ocular domain [22]. However, they can clearly have a longer-lasting effect, exemplified in the study comparing the immediate effect of topical agents (olopatadine) with oral antihistamines (loratadine) [23,24]. Therefore, focus on the development of topical antihistamine agents has increased since 1990.

In a human study, chlorpheniramine, dexbrompheniramine, pyrilamine, and pheniramine significantly reduced the classic histamine-induced conjunctival injection [25,26]. However, the newer second-generation H_1 receptor antagonists have less sedative or anticholinergic effects than earlier compounds [27]. In the human conjunctiva, H_1 stimulation principally mediates the symptom of pruritus, whereas the H_2 receptor seems to be clinically involved in vasodilation [28,29]. The improved effect with H_1 and H_2 blockade was also noted in an animal model using pyrilamine and cimetidine. This study showed histamine-induced ocular surface erythema being virtually abolished by a combination of cimetidine (H_2 -receptor antagonist) and pyrilamine (H_1 -receptor antagonist), whereas either antagonist administered alone produced no significant reduction [30]. However, the potency of the blockade of the various histamine receptors with the newer topical agents has not been well defined. Although topical antihistamines can be used alone to treat allergic conjunctivitis, they have been shown to have a synergistic effect when used in combination with a vasoconstrictor, similar to the addition of a decongestant in the oral formulations for treating allergic rhinitis [13].

Oral antihistamines

Although studies commonly link oral antihistamine use in the treatment of allergic conjunctivitis to its effect on allergic rhinitis, many show conflicting results regarding their impact on the ocular domain of allergy. For example, in one double-blind, placebo-controlled trial evaluating the efficacy of once-daily cetirizine on various symptoms of rhinitis, including nasal congestion, postnasal discharge, sneezing, rhinorrhea, and nasal itching, and ocular

symptoms, including lacrimation and epiphora, showed that all nasal symptoms were positively affected, whereas the ocular symptoms were not [31]. However, in a conjunctival provocation model, cetirizine showed efficacy against symptoms of allergic conjunctivitis [32,33]. In a double-blind conjunctival provocation study, cetirizine administered orally (10 mg twice daily for 4 days) increased the threshold of grass allergen compared with placebo ($P < .004$) by inhibiting redness and itching of the eye [32]. Other studies of oral antihistamines have shown loratadine to have a protective effect in conjunctival provocation tests [34], and desloratadine [35] and fexofenadine [36,37] to significantly reduce ocular symptoms of seasonal allergy rhinitis in placebo-controlled studies. In another study, loratadine was found to increase the allergen threshold in conjunctival provocation tests to 3 to 10 times the baseline level in 60% (6/10) of patients [34]. Other antiallergic drugs under investigation show promising results in the treatment of allergic conjunctivitis; including emedastine, a selective blocker of the H_1 histamine receptor [38].

In other human studies, chlorpheniramine, dexbrompheniramine, pyrilamine, and pheniramine significantly reduced histamine-induced and conjunctival injection [25,26]. Second-generation antihistamines can, however, induce ocular drying [39,40], which may impair the protective barrier provided by the ocular tear film and thus actually worsen allergic symptoms. Similarly, the antimuscarinic binding of topical agents may induce a drying effect after chronic use, but recent animal studies show conflicting results regarding whether chronic treatment with topical agents would have a significant clinical effect in patients [41,42]. Therefore, some experts have suggested that the concomitant use of eye drops may treat ocular allergic symptoms more effectively [43]; ketotifen plus desloratadine [44] and olopatadine plus loratadine [45] have been shown to be more effective than either antihistamine alone.

Topical antihistamines

In general, the earlier topical antihistamines were irritating when administered to the eye. Prolonged use of topical antihistamines is associated with the risk for developing sensitivity reactions that can further aggravate ocular allergies. For antihistamines that are nonselective and block muscarinic receptors in addition to H_1 receptors, ciliary muscle paralysis, mydriasis, and photophobia may result. This effect is more pronounced in patients who have lighter irides. Also related to muscarinic receptor blockade is the risk for angle-closure glaucoma, especially in patients who have a history of narrow-angle glaucoma and those who have narrow angles. The mydriatic effect causes the anterior chamber to become shallower, and decreased aqueous humor outflow leads to increased IOP. The classic signs of acute angle-closure glaucoma include headache, blurry vision, nausea, vomiting, and changes in corneal opacity. Histamine-stimulated phosphatidylinositol turnover and cytokine secretion by human conjunctival epithelial cells are

attenuated by compounds with H_1 -antagonist activity. However, antihistaminic potency alone does not predict anti-inflammatory potential [46]. The newer topical antihistamines are more effective and have fewer adverse effects.

Topical antihistamines

Levocabastine

Levocabastine was identified from a series of cyclohexylpiperidine derivatives as a potent antiallergic agent having rapid and long-lasting activity. It was approved in 1994 for the treatment of allergic conjunctivitis. Levocabastine is a cyclohexyl-3-methylpiperidine derivative that has rapid onset and prolonged activity. Absorption of levocabastine after ocular instillation of single doses is incomplete, with the absolute bioavailability estimated to range from 30% to 60% in patients who have SAC and healthy subjects, respectively. On repeated ocular administration, steady-state plasma concentrations were virtually attained within 7 days of dosing in healthy subjects. After active doses are administered, only low levels of levocabastine are found systemically; plasma concentrations of the drug typically do not exceed 1 to 2 ng/mL [47]. The drug does not seem to cause central nervous system depression, sedation, or effects on psychomotor performance, probably because the systemic absorption of levocabastine is low after ocular instillation [48]. The elimination half-life of levocabastine ranges from 35 to 40 hours after ocular or oral administration and is similar for single and repeated doses. In vitro studies indicated the high selective binding affinity of levocabastine for H_1 receptors along with its exceptionally slow rate of dissociation from these receptors [49]. Levocabastine (dissociation constant, 52.6 nmol/L) exhibited greater functional activity (50% inhibitory concentration, 8–25 nmol/L) than either antazoline or pheniramine [50].

In an ocular provocation study, 10 of 11 patients treated with levocabastine required a 10-fold increase in allergen to reproduce the same symptoms, although pretreatment with an antihistamine caused an increase in late-phase symptoms in 3 of the 11 patients [51].

Emedastine

Emedastine is a selective H_1 antagonist with no apparent effect on adrenergic, dopaminergic, or serotonin receptors [38]. It was the most potent in ligand binding, phosphatidylinositol turnover, and interleukin (IL)-6 secretion, with dissociation constant and 50% inhibitory concentrations of 1 to 3 nmol/L [52]. In human volunteers dosed bilaterally twice daily for 15 days with 0.05% emedastine fumarate ophthalmic solution, plasma concentrations of the parent compound were generally below the limit of the assay. Relief of the signs and symptoms of allergic conjunctivitis have been shown in patients treated for 6 weeks with emedastine in an environmental study, as has

reduction in ocular itching when patients were challenged with antigen at either 10 minutes or 4 hours after dosing with 0.005%/0.05% and 0.05% solutions, respectively. Antazoline hydrochloride, emedastine difumarate, levocabastine hydrochloride, olopatadine hydrochloride, and pheniramine maleate attenuated histamine-stimulated phosphatidylinositol turnover and IL-6 and IL-8 secretion [50]. In another study on conjunctival fibroblasts stimulated with histamine, emedastine significantly reduced production of IL-1, IL-6, and IL-8, whereas azelastine reduced only IL-1 [53]. Clinically, emedastine was similar to ketotifen in a conjunctival provocation model effect on ocular itching [54].

Mast cell-stabilizing agents

Cromoglycate

The prototypic mast cell mediator, cromolyn sodium, has been on the market intermittently in the United States. Its efficacy seems to be concentration-dependent, with a 1% solution having no effect, a 2% solution having a possible effect, and a 4% solution having a probable effect [55]. After many years of clinical use, the possible mechanisms for cromolyn are still not clearly defined. Initially, cromolyn was believed to affect phosphodiesterase or cyclic AMP and B lymphocytes switching from mu (IgM) to epsilon (IgE) heavy chains, which would be a novel potential mechanism for the prevention of mast cell-mediated disorders [56,57]. Sodium cromoglycate was originally approved for more severe forms of conjunctivitis (GPC, AKC, VKC), but many physicians had extended its use to the treatment of allergic conjunctivitis with an excellent safety record, although the original studies reflecting its clinical efficacy showed marginal benefit for allergic conjunctivitis when compared with placebo [58,59].

However, in a study using an opiate conjunctival provocation, prior treatment with cromolyn inhibited ocular mast cell activation, but not necessarily clinical symptoms [60]. A study using topical cromolyn during ragweed season found that the diary eye symptoms were similar among patients using cromolyn on a routine basis (four times daily) and those using cromolyn as needed [61]. However, the regular treatment group had better quality of life with topical cromolyn, whereas the as-needed group showed a trend toward more oral terfenadine use for uncontrolled eye symptoms. Cromolyn effects are not present until 2 to 5 days after the initiation of therapy, with maximum improvement of ocular symptoms noted 15 days after initiation of therapy. Topical cromolyn sodium is equivalent to placebo during the first days of treatment.

In multicenter studies of chronic forms of ocular allergy, vernal conjunctivitis topical cromolyn showed effectiveness in relieving discharge, photophobia, hyperemia, and edema of the eyelids. Itching and changes in visual acuity improvement were equivocal in some studies. However, most studies have shown a lack of efficacy in the major problem associated with vernal

conjunctivitis: papillary hypertrophy of the upper tarsal conjunctiva. In the treatment of giant papillary conjunctivitis, patients experienced symptomatic improvement, but little if any change in ocular signs. In AKC, significant improvement was seen after 4 weeks of treatment with ocular cromolyn in the clinical scores for photophobia, discharge, papillary hypertrophy, limbal changes, and corneal changes and the overall clinical assessments of patients. Another study comparing the effects of topical cromolyn with other immunomodulatory agents (cyclosporine and dexamethasone) showed that cromolyn was ineffective after 14 days of treatment with regard to symptoms or the tear levels of eosinophil cationic protein [62].

Cromolyn has also been used in comparison studies and shown to have similar effect to azelastine, with more than 80% improvement compared with the placebo effect of 50% [63]. A comparison study with olopatadine also showed equivalent results between the agents [64].

Cromolyn sodium 4% ophthalmic solution should be applied four to six times daily, with the dosage decreased incrementally to twice daily as symptoms permit. The major adverse effect is burning and stinging, which has been reported in 13% to 77% of patients. This agent is commonly initiated in patients who have moderate symptoms soon after ocular decongestants are administered for immediate relief [59]. Acute chemotic reactions have been reported with cromolyn [65]. The nasal solution of cromolyn sodium is composed in the exact formulation as the ocular solution, except for the additional sterilization procedure required for ophthalmic preparations. Many physicians have used the nasal solution in the eye, making a concerted effort to keep the medication refrigerated and discard it after 4 weeks to decrease the possibility of bacterial contamination. An allergic reaction to topical disodium cromoglycate was reported, which was proven with skin prick tests, conjunctival provocation tests, and circulating IgE-specific antibodies to disodium cromoglycate [66].

Lodoxamide

Lodoxamide is a mast cell stabilizer that has been shown to be approximately 2500 times more potent than cromolyn in preventing histamine release in several animal models [67,68]. Lodoxamide reduced tryptase levels and decreased the recruitment of inflammatory cells in the tear fluid after allergen challenge [69], and has been shown deliver greater and earlier relief in patients who have more chronic forms of conjunctivitis (eg, VKC, AKC, GPC) than cromolyn [70,71]. However, in a study of allergic conjunctivitis, it was only perceived to be clinically better by the patient, and not the physician. Lodoxamide was more effective than placebo [72] and as effective as levocabastine [73]. In patients who have allergic conjunctivitis, its clinical efficacy vis-à-vis cromolyn remains unclear. It has recently been approved for the treatment of all forms of vernal conjunctivitis at a concentration of 0.1% four times daily. Lodoxamide may be used continuously for 3 months. It has

been labeled as a schedule B drug for use in pregnancy. It can be used in children from 2 years of age. Tear eosinophil cationic protein (ECP) has also been shown to be a marker for eosinophil activation in ocular allergic disorders and has been used to evaluate the efficacy of lodoxamide and sodium cromoglycate in the treatment of VKC. ECP levels were significantly correlated with signs, symptoms, corneal involvement, and number of eosinophils in tears. Sodium cromoglycate did not prevent tear ECP from increasing, whereas lodoxamide therapy significantly reduced ECP tear levels and thus eosinophil activation, and was more effective than disodium cromoglycate in reducing clinical signs and symptoms [74]. In patients who had VKC, median tear leukotriene B₄ and C₄ decreased after treatment with disodium cromoglycate 2%, lodoxamide 0.1%, and fluorometholone 0.1% [75]. In the treatment of various forms of VKC, the lodoxamide group experienced a 67% improvement compared with those using topical cyclosporin A [76].

Pemirolast

Pemirolast potassium was originally marketed as a tablet in Japan in 1991 for treating bronchial asthma and allergic rhinitis, and was subsequently developed and registered in Japan as an ophthalmic formulation for the treatment of seasonal allergic and vernal conjunctivitis. It has been studied in children as young as 2 years of age, with no reports of serious adverse events. Antiallergic pharmacology studies have shown that pemirolast is a specific inhibitor of mast cell degranulation inhibiting the release of chemical mediators, such as histamine. In vitro and in vivo studies have shown that the dose-dependent inhibition of antigen-induced chemical mediators is achieved through interference with mediator release, perhaps from the inhibition of phospholipid byproducts involved in intracellular transduction. Ocular anti-allergic pharmacology testing has shown that ocular instillation of pemirolast seems to have a potent inhibitor effect on the rat conjunctival IgE–mast cell allergy model. Its potency is more than 100 times that of cromoglycate. In a placebo-controlled study evaluating pemirolast 0.1% four times daily, beginning approximately 1 to 2 weeks before the onset of ragweed season and continuing until after the first killing frost (12–17 weeks duration), patients recorded their daily evaluations of ocular itching in a diary. After the allergy season, patients underwent a second CAC. Evaluable patients ($n = 265$) recorded a total of 21,491 patient-days of ocular itching data during allergy season. In every 7- or 14-day period, patients treated with pemirolast potassium 0.1% reported more days without any ocular itching compared with patients receiving placebo. Differences favoring pemirolast potassium 0.1% were statistically significant in 63% (10/16) of all 7-day periods ($P < .046$) and 88% (7/8) of all 14-day periods ($P < .016$). After the allergy season, pemirolast potassium 0.1% was significantly superior to placebo in relieving CAC-induced ocular itching, with relief occurring as early as 3 minutes after allergen challenge ($P \leq .034$) [77].

In the specific evaluation of histamine release from the conjunctiva, the simultaneous use of levocabastine and pemirolast significantly decreased histamine content compared with either levocabastine and pemirolast alone. These findings suggest levocabastine not only had antihistaminic activity but also inhibited histamine release [78]. In a pharmaceutical-sponsored study, cromolyn and pemirolast (100 nM–1 mM) failed to significantly inhibit histamine release from human conjunctival mast cells using exposure times of 1 and 15 minutes before challenge, whereas olopatadine did [79]. This finding suggests discordances between in vitro and in vivo studies even while using the human model, and that some antiallergy agents may have more than one mechanism of action.

Nonsteroidal antiinflammatory agents

Ketorolac

Ketorolac tromethamine (Acular), approved in November 1992, is one of the earliest prescription products for treating itch associated with allergic conjunctivitis. Ketorolac, which is a pyrazolone, is a nonsteroidal anti-inflammatory agent. Its primary mechanism of action is on the arachidonic acid cascade, where it binds cyclooxygenase to block the production of prostaglandins, but it does not inhibit lipoxygenase or the formation of leukotrienes. Prostaglandins, particularly PGE₂ and PGI₂, are extremely pruritogenic to the conjunctival mucosa [80–82]. Clinical studies have shown that topical NSAIDs significantly diminish the ocular itching and conjunctival hyperemia associated with seasonal antigen-induced allergic conjunctivitis [83] and VKC [84]. Unlike topical corticosteroids, these agents do not mask ocular infections, affect wound healing, increase IOP, or contribute to cataract formation. In a recent study on measles conjunctivitis, it helped decrease the amount of hyperemia and was not associated with any viral spread [85,86].

Although topical ketorolac is currently the only topical NSAID approved by the FDA for use in acute SAC, topical diclofenac may have similar features in the treatment of seasonal allergic conjunctivitis [87]. Ketorolac has been studied in comparison with topical antihistamines, with better outcomes in some cases [87–90]. In a recent study compared topical ketorolac with levocabastine in which the medications were instilled in each eye four times daily for 6 weeks, ketorolac produced the greatest improvements in most efficacy variables, followed by levocabastine and vehicle. Ketorolac was significantly more effective than vehicle in reducing mean itching scores, palpebral hyperemia, bulbar hyperemia, and edema [88]. An experimental model of contact lens-induced conjunctivitis showed that treatment may take up to 2 weeks to have an affect [91]. NSAID-induced asthma does not seem to be a problem, except in patients who have the triad of asthma, nasal polyposis, and aspirin sensitivity [92].

The most frequent adverse events reported with the use of ketorolac ophthalmic solutions (occurring in 40% of patients participating in clinical

trials) have been transient stinging and burning on instillation. Other adverse events occurring approximately 1% to 10% of the time during treatment with ketorolac ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis, and superficial ocular infections. Adverse events reported rarely with the use of ketorolac ophthalmic solutions included corneal infiltrates, corneal ulcer, eye dryness, headaches, and blurred vision. It has been reformulated and is now used to reduce ocular pain after cataract and refractive surgery [93].

Multiple action agents

Olopatadine

Olopatadine (Patanol, Pataday) seems to possess a dual form of action with limited mast cell stabilizing effects and H_1 -receptor binding [52,79,94]. Compared with the first-generation antihistamines (antazoline and pheniramine), olopatadine was also noted to inhibit cytokine secretion [52], including tumor necrosis factor (TNF)- α mediator release from human conjunctival mast cells [95–97]. Olopatadine was approximately 10-fold more potent as an inhibitor of cytokine secretion (50% inhibitory concentration, 1.7–5.5 nmol/L) than predicted from binding data, whereas antazoline and pheniramine were far less potent (20- to 140-fold) in functional assays [49]. It has been shown to be significantly more effective than placebo in relieving itching and redness for up to 8 hours [98,99]. Olopatadine also binds to S100 family of calcium-binding proteins similar to amlexanox [100]. In a comparison study with another multiple-action agent, ketotifen, olopatadine showed only slightly better results over 2 weeks of treatment [101]. In one of the few head-to-head studies using the conjunctival provocation model, olopatadine and azelastine treatments were significantly more effective than placebo at reducing itching postchallenge. Subjects gave itching assessments (scale, 0 = no itching to 4 = severe itching) every 30 seconds for 20 minutes (Olopatadine was significantly more effective than azelastine in reducing itching at 3.5 minutes through 20 minutes postchallenge [102].

Ketotifen

Ketotifen (Zaditor), a benzocycloheptathiophene agent, has been used as an orally active prophylactic agent to manage bronchial asthma and allergic disorders. Ketotifen has shown pronounced antihistaminic and antianaphylactic properties, resulting in moderate to marked symptom improvement in most patients who have atopic dermatitis, seasonal or perennial rhinitis, allergic conjunctivitis, chronic or acute urticaria, or food allergy [103]. It recently became generic and is available over-the-counter for treating allergic conjunctivitis. Ketotifen is distinguished from the cromones, sodium cromoglycate and nedocromil, by a conjoint mast cell stabilizing effect; several

antimediator properties, including strong H_1 -receptor antagonism [104,105]; and inhibition of leukotriene formation [86,106]. A possible effect of ketotifen on the constitutive eosinophil apoptosis and IL-5-mediated eosinophil survival has been postulated to be more induction of primary necrosis than apoptosis [107]. In the guinea pig model, ketotifen was more effective than olopatadine and levocabastine in reducing conjunctival edema and vascular permeability as measured by Evans blue dye leakage in eyelids and eyeballs [108].

In an experimental model for allergic conjunctivitis, chlorpheniramine, ketotifen, and levocabastine were effective in inhibiting cedar pollen-induced conjunctivitis [109]. In the standard CAC model comparing ketotifen with placebo, ketotifen showed up to a 30% decrease in signs and symptom associated with allergic conjunctivitis and a lack of tachyphylaxis over the course of 4 weeks [110]. In another rare head-to-head study of two topical agents (without a placebo control), levocabastine hydrochloride ophthalmic suspension and ketotifen fumarate ophthalmic solution were respectively instilled in the left and right eyes, which were then challenged with the allergen. Pollen allergen-induced ocular symptoms were itching and hyperemia of the palpebral conjunctiva, and itching lasted for more than 5 hours. Moreover, preadministration of antihistamine eye drops suppressed the increases in the ocular symptom scores, eliminating itching within 1 hour. Allergen provoked not only ocular symptoms but also nasal symptoms in 78% of patients [111]. However, ketotifen was not better than a topical cromolyn-chlorpheniramine combination at preventing itching and redness in the CAC model [112].

One study randomly assigned patients who had SAC to one of three groups: two drops per eye twice daily for 30 days of either topical ketotifen 0.025% ophthalmic solution, olopatadine 0.1% ophthalmic solution, or placebo. Clinical scores (itching, tearing, redness, eyelid, swelling, and chemosis) and conjunctival impression cytology specimens were performed on day 0 of the study (baseline), day 15, and day 30. The percentages of cells expressing intercellular adhesion molecule 1, vascular cell adhesion molecule (CAM)-1, human leukocyte antigen (HLA)-DR, and beta 1 integrin (CD29) from conjunctival impression cytology specimens were determined using flow cytometry. Both active-treatment groups noted significant improvements in clinical scores (tearing and itching) and reduction in the expression rates of CAMs and inflammatory markers in conjunctival surface cells within a month [113]. However, in a double-blinded preference study, olopatadine was chosen more than ketotifen [114], perhaps because several studies have reported that ketotifen has a mild stinging affect on the conjunctival surface [104].

Nedocromil

Nedocromil is a pyranoquinoline dicarboxylic acid that was originally believed to be just a mast cell stabilizing agent but is now appreciated to

have multiple actions [115], including as an H₁ antagonist with inhibitory effects on various allergic inflammatory cells, mast cells, and eosinophils [116], but with conflicting results on the inhibition of neutrophil migration [117,118]. Nedocromil seems able to stabilize mast cells and inhibit histamine release more than cromolyn [116]. Various studies have suggested that nedocromil may have its effect on B lymphocytes switching from μ (IgM) to ϵ (IgE) heavy chains, similar to studies for its chemistry-related cousin, cromolyn [56,57,119]. In an animal model, nedocromil was shown to suppress early- and late-phase conjunctival hyperemia, conjunctival edema, eyelid edema, and eosinophil infiltration [120]. Topical nedocromil treatment has been shown in an ocular allergen challenge model to reduce tear concentrations of histamine and prostaglandin D₂ and the number of 3H4-positive mast cells (purportedly the secreted form of IL-4) [121] while increasing the conjunctival tolerance to the allergen [122]. In cultures, nedocromil was shown to abolish the expression of HLA-DR and reduce intracellular adhesion molecule (ICAM)-1 expression [123].

Compared with placebo, nedocromil showed improved control of ocular pruritus and irritation associated with SAC [124–130] and vernal conjunctivitis [131]. In a study involving patients who had PAC, nedocromil eye drops were clinically effective in controlling symptoms that persisted despite previous treatment with cromoglycate [132]. The results of several placebo-controlled studies have shown that nedocromil is effective in alleviating the signs and symptoms of SAC and provide relief in 80% of patients [133,134]. Its safety profile is similar to that of sodium cromoglycate, but it seems to be more potent in treating chronic ocular allergic conditions, such as VKC. In a comparative study, nedocromil sodium 2% eye drops were more efficacious than sodium cromoglycate for treating hyperemia, keratitis, papillae, and pannus and had a quicker effect on itching, grittiness, hyperemia, and keratitis [133]. Nedocromil can be given just twice daily [132] and is associated with stinging or burning of the eyes on application of the drops and a distinctive taste in 5% of the population [135].

Azelastine

Azelastine, which has a half-life of approximately 22 hours, is a second-generation H₁-receptor antagonist that is primarily administered intranasally, although an oral formulation is used in some countries for effective relief of symptoms of allergic rhinitis after oral or intranasal administration [136,137] with a secondary entry in the topical treatment of allergic conjunctivitis [105,138].

Azelastine has been reported to inhibit early allergic response [139,140] and histamine release from rat mast cells after antigen and nonantigen stimuli [140–142], and seems to inhibit IgE secretion from IgE-producing hybridoma FE-3 cells through preventing C-epsilon mRNA expression [143]. The additional prophylactic antiallergic properties are probably partially caused by

the inhibition of a broad array of other inflammatory mediators and important receptors for the allergic response, inhibition of superoxide generation by neutrophils and eosinophils [144], inhibition of leukotriene synthesis [145–150], inhibition of TNF- α secretion from rat basophil leukemia cells [151,152] and IL-6 from human leukemic mast cells [96,153], and down-regulation of ICAM-1 in the human conjunctiva [154]. Normal human umbilical cord blood–derived cultured mast cell stimulation with anti-IgE leads to substantial secretion of IL-6, TNF- α , and IL-8, whereas preincubation for 5 minutes resulted in almost maximal inhibition of TNF- α (80%) with 6 μ M azelastine, of IL-6 (83%) with 24 μ M, and of IL-8 (99%) with 60 μ M [155]. When compared with another multiple-action agent in a similar designed experimental model, results with 24 μ M azelastine were similar to those with 133 μ M of olopatadine (a fivefold difference). At this concentration, these drugs inhibited IL-6 release by 83% and 74%, tryptase release by 55% and 79%, and histamine release by 41% and 45%, respectively [156]. Apart from the ability to inhibit histamine release from mast cells and prevent the activation of inflammatory cells, the antiallergic potency of azelastine is probably partially caused by down-regulation of ICAM1 expression during early- and late-phase response that likely leads to reduced inflammatory cell adhesion to epithelial cells, confirming the prophylactic properties of azelastine [154].

These and various other studies have reflected an extensive array of anti-inflammatory mechanisms of azelastine in the control of allergies and asthma, and it is the only nasal antihistamine spray in the United States that is also approved for treating allergic conjunctivitis [157]. In one study [152], azelastine was instilled into the eyes of patients who had rhinoconjunctivitis sensitive to *Parietaria judaica* both before and after antigen-specific conjunctival challenge (ASCC). When applied 30 minutes after ASCC, a statistically significant reduction in total symptom score (conjunctival hyperemia, lacrimation, itching/burning, eyelid swelling) was observed in azelastine-treated eyes compared with those receiving placebo eye drops, beginning 10 minutes after administration and lasting through the final evaluation 20 minutes later. Total symptom scores were also significantly reduced for up to 6 hours in patients treated twice daily with topical azelastine as opposed to placebo for 1 week before ASCC, accompanied by a significant reduction in conjunctival inflammatory cell infiltration. In a pediatric SAC study comparing the effects of azelastine with levocabastine eye drops, the response rate in the group receiving azelastine eye drops was significantly higher (74%) than that in the placebo group (39%) and comparable with that in the levocabastine group (69%) [158].

In a European study, azelastine significantly improved itching and conjunctival redness compared with placebo ($P < .001$). Tolerability was rated good or better by 97% of patients, with a noticeable bitter taste and some application site stinging. On day 7, ocular symptoms score improved by 1.5 ± 0.9 (compared with 0.5 ± 0.8 for placebo) using a six-point scale

with score improvement more than or two in 55% treated with azelastine (versus 14% treated with placebo). Itching and redness further improved at day 42 (score improvement more than two in 95% treated with azelastine versus 33% treated with placebo) and completely resolved for 47% patients treated with azelastine (versus 10% treated with placebo) [159].

Epinastine

Epinastine (Elestat) is a potent histamine H_1 - and H_2 -receptor antagonist with mast cell-stabilizing properties. It inhibits histamine release and has other anti-inflammatory activities, and was recently approved in the United States to prevent itching associated with allergic conjunctivitis (olopatadine once-daily formulation was also recently approved for this purpose). It does not significantly penetrate the blood-brain barrier and its safety and tolerability profiles seem to be equal to those of most other topical antihistamines. It is considered a multiple-action agent. Pretreatment with epinastine significantly reduced histamine and $TNF-\alpha$, whereas IL-5, IL-8, IL-10, and $TNF-\beta$ profiles were differentially decreased. In vivo, pretreatment with epinastine and olopatadine significantly reduced the clinical scores and eosinophil numbers ($n = 6$; $P < .05$), whereas epinastine also reduced neutrophils ($P < .02$), reflecting the existence of different patterns of inflammation inhibition [160]. The role of H_1 -, H_2 -, and H_3 -receptor affinities in actual treatment is unclear, but past clinical experience indicates that the presence of multiple binding may be beneficial. In an animal model of histamine-induced vascular leakage, epinastine, azelastine, and ketotifen had a shorter duration of effect than olopatadine [161]. In a recent review, ketotifen, pyrileamine, and epinastine seemed to have the strongest H_1 and H_2 affinities, although a specific study to determine clinical relevance has not been performed [104].

In a major clinical trial, ophthalmologists performed conjunctival provocations to confirm the diagnosis of SAC. The primary end point was ocular itching, and secondary end points included ocular hyperemia, chemosis, ocular mucous discharge (all assessed on a five-point scale), eyelid swelling (assessed on a four-point scale), and tearing. present or absent). Ocular itching was clearly reduced with epinastine compared with placebo ($P = .045$), but ocular itching and hyperemia scores were similar in the epinastine and levocabastine groups [162]. In the human CAC model, multiple signs and symptoms of allergic conjunctivitis were significantly reduced by instillation of epinastine compared with vehicle. Epinastine showed prompt onset (3 minutes) and long duration of action (≥ 8 hours). Mean severity scores were significantly lower with epinastine compared with vehicle at all time points after onset and duration challenges, including ocular itching ($P < .001$); eyelid swelling ($P < .001$); conjunctival ($P < .001$), episcleral ($P < .001$), and ciliary hyperemia ($P < .001$); and chemosis ($P \leq .009$) [163].

A concern also exists about the impact of many antihistamines, and that multiple-action agents with antihistaminic activity may also show

anticholinergic activity. In a study comparing loratadine and epinastine, anticholinergic activity was noted to affect the eyes after 4 days of treatment, and loratadine was associated with clinical signs of ocular dryness, including decreased tear volume and tear flow, in contrast with topical epinastine [164]. In a longer (1 month) head-to-head comparison of olopatadine and epinastine in a botulinum toxin B-induced murine model for dry eye, no difference was noted [41], whereas another animal model found epinastine to be superior [42].

Mizolastine

Mizolastine, a benzimidazole derivative, is a second-generation antihistamine that has been shown in experimental studies to possess 5-lipoxygenase inhibitory properties in addition to its H₁-receptor antagonistic activity [165,166]. It has been shown to interrupt intermediate signaling events that regulate cell function, such as through exerting an inhibitory effect on protein kinase C (PKC) activation in a dose-dependent manner [167]. Mizolastine has a terminal beta half-life of approximately 1 hour and a duration of action of at least 2 hours. The compound did not show any anticholinergic effects in a standard animal model using carbachol [168]. Mizolastine has a pronounced effect on nasal blockade that is believed to be linked to its anti-inflammatory properties. European approval for the treatment of perennial allergic rhinoconjunctivitis has shown some beneficial effects on ocular and total nasal scores after 6 months of treatment [165].

In an evaluation of mizolastine's effect on ocular allergy inflammation, it decreased the mean ocular symptom score (which included itching, tearing, and erythema) as reported by patients and physicians by 40% compared with 7% in the placebo group [169]. The decrease was noted within the first 2 weeks and continued for the remainder of the 4-week study. In a 2-week study, mizolastine reduced total symptom scores, nasal scores, and ocular scores at the end of the first week [170]. In perennial allergic rhinitis, mizolastine significantly improved symptoms of nasal obstruction compared with placebo and also significantly reduced nasal membrane color, nasal secretions, and mucosal swelling as shown with rhinoscopy. These effects were maintained over a 5-month treatment period [171]. Mizolastine was shown to have an effect within 1 hour in 50% of patients, and 78% of patients reported a positive effect after the first intake [172]. In another study, mizolastine showed more symptom relief with the first 3 days than cetirizine [173].

Picumast

Picumast dihydrochloride (3,4-dimethyl-7-[4-(4-chlorobenzyl) piperazine-1-yl] propoxycoumarin dihydrochloride) is a compound that seems to have prophylactically active antiallergic properties, which combines inhibition of mediator release and action on H₁-antagonism (and that of its metabolites on M2 and M1 receptors). It was originally believed to have potential in the treatment of bronchial and allergic rhinitis but was found to have limited

effect [174,175]. Because the activity profile of picumast differs clearly from that of known prophylactic antiallergic drugs such as cromolyn and ketotifen, as reflected in the systemic administration of picumast in the inhibition of the allergen-induced conjunctivitis model when compared with mepyr-amine and ketotifen, an ocular formulation was further evaluated [176]. Examination of any specific long-term effects on the lens did not show any opacifications after 1 year of study comparing ketotifen with picumast [177].

Amlexanox

Amlexanox, an azoxanthone derivative that was developed as an ocular antiallergic drug, has shown limited antihistamine properties in guinea pig models of allergic conjunctivitis [109,178–180]. One target is believed to be a heat shock protein because it binds directly to wild-type Hsp90 through the *N*- and *C*-terminal domains [181] and to the S100 family of calcium-binding proteins, a multigenic family of low-molecular-weight Ca(2+)-binding proteins comprising 19 members [100]. It was recently found to inhibit the formation of the fibroblast growth factor (FGF-1), which led to its present position in investigational research in the treatment of aphthous ulcers [182] and is now available as Aphthasol. Although a high concentration was needed, tranilast and amlexanox showed significant inhibition of cedar pollen-induced conjunctivitis (Table 1) [109].

Table 1

Effects of the inflammatory cascade in treating allergic conjunctivitis: several of the more commonly used multiple-action agents

	Azelastine HCl 0.05% (Optivar)	Epinastine HCl 0.05% (Elestat)	Ketotifen fumarate 0.25% (Zaditor) ^a	Olopatadine HCl 0.2% (Pataday)
Indication	Relief of itching associated with allergic conjunctivitis	Relief of itching associated with allergic conjunctivitis	Temporary prevention of itching of the eye caused by allergies	Relief of itching associated with allergic conjunctivitis
Dosage	One drop bid each affected eye	One drop bid each affected eye (≥ 3 years of age)	One drop q8–12h each affected eye	One drop qd each affected eye
Adverse effects	Transient sting (~30%) headache (~15%) bitter taste (~10%)	Cold symptoms (~10%) upper respiratory infection (~10%)	Headache (~10%–25%) conjunctival injection (~10%–25%) rhinitis (~10%–25%)	Cold syndrome (~10%) pharyngitis (~10%)

^a Ketotifen (Zaditor) is now available over-the-counter in the United States.

Topical antihistamines and dry eye

Because all topical antihistamines are also known to have muscarinic binding abilities and may theoretically cause dry eye syndrome complaints with chronic use, an animal model was used to compare the effects of topical olopatadine, epinastine, and lubricant eye drops on dry eye ocular surface disease in the botulinum toxin B-induced mouse model of keratoconjunctivitis sicca. In this model, no statistically significant differences were seen in aqueous tear production among the three different medication groups at all time points throughout the 4-week experimental period. In addition, changes in corneal fluorescein staining of the olopatadine group versus the epinastine group did not show a statistically significant difference. In this botulinum model, the additional placement of topical olopatadine and epinastine does not seem to cause significantly additional damage to the compromised ocular surface secondary to dry eye after continuous 4-week, twice-daily application [41]. However, on examining other animal models, epinastine-treated mice after 2 days showed greater mean tear volumes than olopatadine-treated mice at 15, 45, 90, and 240 minutes, with statistical significance at 15 and 45 minutes ($P < .001$). Olopatadine significantly reduced tear volume compared with untreated controls at 15 and 45 minutes ($P < .001$). After 4 days, tear volumes with epinastine treatment exceeded those with olopatadine treatment at all time points, with statistical significance at 45 minutes ($P < .05$) [42]. Therefore, which of these models has clinical relevance in patients who have ocular allergies remains to be determined.

Steroids

Ophthalmic steroids

Topical corticosteroids are appropriate for treating severe allergic conjunctivitis because of their potent antiinflammatory effect. Corticosteroids block most inflammatory pathways in the allergic reaction, especially the late-phase mediators that perpetuate the persistent and chronic forms of ocular allergy [5,6].

Corticosteroids are divided into ketone and ester corticosteroids and are most commonly used for treating ocular inflammation. Conventional corticosteroids, such as prednisolone and dexamethasone, have a ketone group at the C-20 position that is associated with cataract formation. Substitution of the C-20 group with a chloromethyl ester moiety led to development of loteprednol etabonate (Alrex), currently the only ester corticosteroid approved for treating the signs and symptoms of SAC [183]. Loteprednol etabonate has several potential advantages over ketone corticosteroids. First, loteprednol etabonate has high lipophilicity compared with ketone corticosteroids, which may increase its efficacy by enhancing penetration into target inflammatory cells [184]. Second, loteprednol etabonate's potential for inducing ocular hypertension is minimized by its rapid conversion to

inactive metabolites after achieving its therapeutic role [185]. Third, low levels of loteprednol etabonate are detected in plasma, which reduces systemic side effects.

Data from clinical trials in patients who have allergic conjunctivitis show that topical loteprednol etabonate is a safe treatment option. In a placebo-controlled study of giant papillary conjunctivitis, no significant change in IOP was seen after 4 weeks of loteprednol etabonate 0.5% compared with baseline [186]. Data from two 6-week placebo-controlled studies of patients who had SAC showed more effective reduction of symptoms in the group treated with loteprednol etabonate compared with the placebo group [187–189]. A unique feature of loteprednol is the claim that it is a *site-specific* steroid, meaning that the active drug resides at the target tissue long enough to render a therapeutic effect but not long enough to cause the secondary harmful effects of, for example, increased IOP [190,191].

Topical corticosteroids have the potential to induce serious side effects, such as cataracts, elevated IOP, and infection. Therefore, topical corticosteroids are best used over short periods (up to 2 weeks); IOP and lens clarity should be monitored in use beyond 2 weeks. They should not be used in conjunction with a topical antibiotic because if infection is a concern, it may be viral and topical steroids would be contraindicated unless an eye care specialist examines the infection with a biomicroscope.

Intranasal steroids

Increasing evidence supports the effect of intranasal corticosteroids on reducing ocular symptoms associated with allergic rhinitis. Initial evidence for this therapeutic benefit surfaced during placebo-controlled clinical trials studying the effects of intranasal corticosteroids on a spectrum of allergic rhinitis symptoms [192–194]. More recently, studies designed specifically to investigate effects on ocular symptoms have reinforced those observations [195,196]. In a pooled analysis of data from seven randomized placebo-controlled clinical trials of intranasal fluticasone propionate in seasonal allergy rhinitis, both subject and physician ratings of ocular symptom severity on study days 7 and 14 also favored intranasal fluticasone [196].

Not only have intranasal corticosteroids been shown to be superior to placebo in reducing ocular symptoms of allergic rhinitis but also accumulating data suggest that they are comparable to or possibly more effective than oral antihistamines. A meta-analysis of 11 randomized controlled trials found no significant difference in improvement of eye symptoms between intranasal corticosteroids and oral antihistamines [197]. A similar meta-analysis of 10 randomized clinical trials failed to identify any significant difference in ocular symptom relief between intranasal corticosteroids and nonsedating antihistamines [198], suggesting that intranasal corticosteroids are equivalent to oral antihistamines in their effect on the eye or that antihistamines do not work on ocular allergy. However, more recent studies have shown that

intranasal steroids may be a class effect on ocular allergy, because triamcinolone [199], beclomethasone [200], budesonide [201], fluticasone propionate [195], fluticasone furoate [202] and mometasone furoate have shown this activity [203].

Immunomodulatory agents

Cyclosporine

Although cyclosporine (CsA) has been available for more than 20 years in various areas of organ transplantation, its lipophilicity presented a unique challenge for generating a solution or suspension to be delivered to ocular surface [204]. In an animal model, CsA 0.1% and 0.5% eye drops significantly inhibited eosinophilic infiltration into the conjunctiva in mice actively immunized with ragweed compared with vehicle-treated mice, and the inhibition was similar to that induced with 0.1% betamethasone [205]. Patients who had severe VKC treated with topical 2% cyclosporine A in preservative-free artificial tears showed improved signs and symptoms, and experienced no side effects during the 14-week study [206]. In a lower dose regimen, 0.05% cyclosporine A for steroid-dependent AKC and VKC showed no benefit over placebo as a steroid-sparing agent [207]. Compared with a 0.5% solution of ketorolac, CsA 0.5% had a slower onset of improvement over 2 to 4 weeks, with a significant difference in subjective ($P < .005$) and objective ($P < .001$) scores seen between the eyes treated with CsA or placebo at 2 weeks. At 4 weeks, scores for signs ($P < .001$) and symptoms ($P = .01$) were reduced in the placebo-treated eyes, with no further improvement in the CsA-treated eyes [208].

Immunotherapy

Immunotherapy was used for the primary treatment of allergies, or spring “catarrh,” before antihistamines and other pharmacologic agents were discovered. In the original report, allergen immunotherapy “measured the patient’s resistance during experiments of pollen extracts to excite a *conjunctival* reaction” [209]. The eye, and not the skin, was the target organ.

The efficacy of allergen immunotherapy is well established, although allergic rhinitis seems to respond better to treatment compared with allergic conjunctivitis. In patients who experienced allergic asthma and rhinoconjunctivitis when exposed to specific animal dander (Fel d I allergen), one study showed that immunotherapy improved overall symptoms of rhinoconjunctivitis, decreased antiallergy medications, and required a 1-log (10-fold) increase in the dose of allergen to induce a positive ocular challenge test reaction after 1 year of immunotherapy with the cat allergen [210]. This finding was also noted in an immunotherapy study over 12 months with a purified and standardized preparation of *Dermatophagoides farinae*, in which patients receiving immunotherapy injections experienced

significant improvement in their subjective symptoms ($P < .028$) and objective cutaneous ($P < .0001$) and conjunctival ($P < .001$) sensitivities. Subjective improvements also correlated well with changes in conjunctival ($P < .01$), and especially skin sensitivity ($P < .005$), subjective improvement [211]. However, whether ocular or nasal symptoms are more responsive is unclear, because the studies were not designed with well-defined patient groups; nor is the natural history of nasal and ocular allergy known. As shown in patients sensitive to ragweed treated for at least 2 years with specific ragweed immunotherapy, symptom assessment postchallenge revealed that nasal symptoms responded more than ocular symptoms when compared with controls [212]. Although initial studies of allergen immunotherapy did not specifically address ocular symptoms in a separate manner [213], more-recent clinical studies have begun to identify improvement in ocular signs and symptoms in a separate category [214–216], including the standard use of subcutaneous immunotherapy [217] and the investigational forms of sublingual immunotherapy [218–220]. In a more recent study, the clinical effect on rhinitis and conjunctivitis achieved during specific subcutaneous immunotherapy even persisted for years after termination of treatment (5-year follow-up). The visual analog scale reflected an two- to threefold improvement for ocular ($P < .001$) and nasal scores ($P < .01$), whereas the conjunctival sensitivity measured with provocation tests were significantly reduced by more than 2-logs of allergen from years 2 to 5 ($P < .001$) [221].

Summary

Pharmacologic treatment of allergic conjunctivitis consists of agents designed to block various pathways in the IgE–mast cell mediated inflammatory cascade. Oral and topical antihistamines target histamine receptors, preventing histamine-mediated symptoms of allergic conjunctivitis, such as itching, watery eyes, chemosis, and periorbital swelling. Antihistamines may have a minimal effect on inflammatory mediators and tend to induce ocular drying, which may limit use. Although topical mast cell stabilizers block the release of histamine, prostaglandins, and leukotrienes through stabilizing mast cell membranes, they are more useful as prophylaxis because they have no effect on already-synthesized inflammatory mediators. Topical multiple-action agents with mast-cell–stabilizing activity have more diverse inhibitory effects on the inflammatory cascade, and will inhibit pre-existing inflammatory mediators and block synthesis of more inflammatory mediators. Because of their ability to block the generation of most inflammatory mediators through inhibition of mast cell phospholipase A2, topical corticosteroids are the most effective treatment for persistent and chronic forms of allergic conjunctivitis. However, corticosteroids are less likely to be prescribed because of their increased risk for cataract formation and elevated IOP, and their restriction to short-term use. According to current treatment recommendations, allergic conjunctivitis is managed in a stepwise

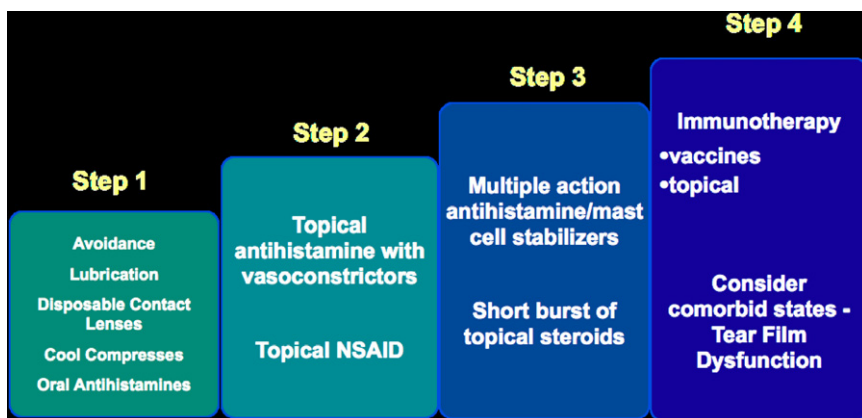


Fig. 2. Stepwise treatment. NSAID, nonsteroidal anti-inflammatory drug.

approach (Fig. 2). Lubricants are initially recommended for disease prevention. In patients who do not experience response, pharmacotherapy is prescribed in the following sequence until acceptable relief of symptoms is achieved: (1) topical antihistamines, alone or in combination with nonsteroidal antiinflammatory drugs; (2) topical antihistamines combined with vasoconstrictors; and (3) multiple-action agents with a short course of corticosteroids.

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