Topical antihistamines, mast cell stabilizers, and dual-action agents in ocular allergy: current trends

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Purpose of review
To address the current trends of therapeutic mechanisms for treatment of allergic conjunctivitis (AC), based on topical antihistamines and mast cell stabilizers (MCS).

Recent findings
The antihistamine drug alcaftadine has H4 receptor inverse agonism, anti-inflammatory and MCS activities. The antihistamines levocabastine and azelastine are more effective than placebo in treatment of AC symptoms in randomized controlled trials (RCTs). The topical dual-action antihistamines/MCS olopatadine, azelastine, ketotifen, and epinastine are commonly used in Europe and in the United States for mild subtypes of AC. For the main symptoms of AC, ocular itch and conjunctival hyperemia, epinastine 0.05% was superior to placebo, but equal or more effective than olopatadine 0.1%, while the later was more effective than ketotifen. High concentration olopatadine 0.77% had longer duration of action, better efficacy on ocular itch, and a similar safety profile to low-concentration olopatadine 0.2%. The new formulas of topical dual-action agents present longer duration of action, leading to a decreased frequency of use.

Summary
The topical dual-action agents are the most effective agents treating signs and symptoms of mild forms of AC. There is superiority to the high-concentration olopatadine drug over other agents on ocular itch, with prolonged effect when used once-daily.

Keywords
antihistamines, dual-action, mast cell stabilizers, ocular allergy, treatment

INTRODUCTION

Allergic diseases affect one third of the world population, with an estimated 40–60% of these cases having ocular involvement [1]. Allergic conjunctivitis is one of the most common ocular disorders and represents a collection of hypersensitivity conditions that affect the lid and conjunctiva [2]. The estimated incidence of allergic conjunctivitis is ranged between 10 and 36% of the US population [3–5]. AC is classified into seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), contact blepharoconjunctivitis, and giant papillary conjunctivitis (GPC) [2,3]. The most two common subtypes of allergic conjunctivitis, SAC, and PAC are manifested with itching, redness, and tearing, as a result of human bodily exposure to specific allergens [6].

The epidemiology of allergic conjunctivitis was recently reported in an extensive European cohort of research subjects, with the mean age of allergic conjunctivitis patients being 38 ± 19 years. The percentage of subjects with SAC was 55% and was similarly distributed among all age groups, followed by 18% with PAC that increased with age, and 9% with VKC which was common in under the age of 18 [7]. The ocular signs and symptoms of allergic conjunctivitis included ocular itching, conjunctival redness, hyperemia, chemosis, lid skin swelling and keratitis [8–10]. Among the allergens reported to trigger allergic conjunctivitis, there were pollen sensitivities, exposure to nonspecific environmental

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KEY POINTS

- Mild subtypes of allergic conjunctivitis, SAC, and PAC can be treated with nonpharmacological treatments, such as cold compress, topical lubricants, and over-the-counter drugs.
- In mild to moderate cases of SAC and PAC, antihistamines or mast cell stabilizers can be prescribed.
- In severe forms of allergic conjunctivitis, such as atopic keratoconjunctivitis and vernal keratoconjunctivitis, corticosteroids, NSAIDs or immunomodulator agents should be considered.
- The levocabastine and azelastine drugs, with antihistamine effects, had superiority over placebo in RCTs treating allergic conjunctivitis.
- Exclusive treatment with antihistamines or mast cell stabilizers is not sufficient, thus the combined dual-acting agents are the medication of choice.
- The dual-action agents commonly used are olopatadine, azelastine, ketotifen, and epinastine. The new formulas are associated with prolonged duration of action and therefore decrease the frequency of use.

conditions, pollutants, and cigarette smoke. Positive allergy tests to specific allergens were found in 82% out of 3545 patients with history of allergic conjunctivitis [7].

The pathophysiology of allergic conjunctivitis is mediated by immunoglobulin E-related mast cell activation, with release of histamine and other mediators promoting activation of other immune cells and further inflammation [6,11]. The early phase reaction of SAC and PAC lasts about 30 min and includes the interaction of allergens with immunoglobulin E (IgE), leading to IgE cross-linking at the mast cell membrane with degranulation and release of histamine, tryptase, prostaglandins, and leukotrienes. The late phase reaction of mast cell degranulation in the conjunctiva includes the activation of vascular endothelial cells, leading to expression of cellular mediators and activation of inflammatory cells, such as T lymphocytes, eosinophils, and neutrophils. This prolonged phase is associated with severe cases of allergic conjunctivitis [5].

The principal aims of treatment in allergic conjunctivitis are to minimize and control signs and symptoms, such as redness, itching, tearing, and conjunctival swelling, as well as preventing the inflammatory cycle in prolonged and severe cases of allergic conjunctivitis [8]. Currently, the two main therapeutic options for AC are inverse histamine agonists (antihistamines) and mast cell stabilizers, considered better options than anti-inflammatory and immunosuppressant agents [6]. Other avenues of treatments for allergic conjunctivitis are vasoconstrictors, anti-inflammatory agents that include non-steroidal anti-inflammatory drugs and corticosteroids, and in recent years, multiple action and novel immunosuppressive agents such as cyclosporine and tacrolimus, for the chronic forms of allergic conjunctivitis such as AKC, VKC, and GPC [12]. Basic and clinical trials in past years present a better understanding of the pathogenesis of allergic conjunctivitis, leading to the emergence of new pharmacological agents, such as more potent mast cell stabilizers and the dual-action antihistamines/mast cell stabilizers combined agents. This article reviews the current trends and latest data on the most popular and effective treatments for allergic conjunctivitis; the topical anti-H1 agonists and mast cell stabilizers.

ANTIHISTAMINES

In allergic conjunctivitis, the interaction between histamine and its receptor is a main player in the genesis of allergic response. Histamine mediates the tissue response to conditions of mechanical or infectious injury and also may serve as a neurotransmitter for gastric acid secretion [6]. As such, blocking the histamine receptors serves as a primary therapeutic path for topical allergy medications. So far, four histamine receptors H1–H4 have been discovered (H1R, H2R, H3R, and H4R) in conjunctival epithelium and goblet cells [13]. These receptors are associated with conjunctival hyperemia, cytokine secretion, fibroblast proliferation, adhesion molecule expression, microvascular permeability, and production of procollagens [9]. These cellular events, known as the 'early-phase reaction,' lead to classical symptoms of allergic conjunctivitis, such as ocular itching, tearing, burning, redness, and/or eyelid swelling. The early response occurs several minutes after the cross-linking of IgE antibodies to mast cells on the conjunctival tissue. Degranulation of mast cells promotes release of inflammatory mediators, such as histamine, tryptase, proteoglycans, and acid hydrolases. This said, histamine is considered to be the main player in the early-phase reaction [13].

Topical antihistamines agents have demonstrated a significant reduction in signs and symptoms of conjunctival allergies compared with placebo in clinical trials [8], as their main action is to antagonize the vasodilator effects of histamine [6]. Compared with oral antihistamines, the single-acting topical antihistamines also have more rapid

action on allergic conjunctivitis, do not cause sedation, and are also better tolerated by the patients. However, these agents primarily affect the early-phase reaction of allergic conjunctivitis and are contraindicated for closed-angle glaucoma patients [6,8].

The allergic conjunctivitis pharmacotherapy group of drugs includes available antihistamines, such as azelastine, antazoline, pheniramine, levocabastine, emedastine, and bepotastine, which are all competitive blockers of the H1 receptor; some block H2, H3, and/or H4 [9,14]. These drugs are associated with relief of allergic conjunctivitis signs and symptoms, especially decreased ocular itching. However, they also associates with dry eyes due to concomitant anticholnergic and muscarinic-binding effects, like in the desloratidine drug, also have a short duration of action, and often do not provide complete control of the disease with exclusive use [2].

MAST CELL STABILIZERS

Activation of mast cells is a key player in the initiation of allergic response in SAC, PAC, VKC, AKC, and GPC. Cross-linking of IgE molecules on mast cell membranes promotes the release of histamines and inflammatory mediators [11]. Immediate ocular symptoms such as itching and burning are the direct result of mast cell-released histamine and are considered to be cornerstones of the 'early-phase response,' whereas the recruitment of proinflammatory mediators as neutrophils, T cells, basophils, and eosinophils represents the prolonged stage of the conjunctival allergic reaction, as seen in the 'late-phase response' [11]. The acute early-phase response of allergic conjunctivitis consists of release of a broad spectrum of inflammatory mediators and cytokines due to degranulation of mast cells and occurs several minutes after the allergen exposure. However, during the late phase, a recruitment of immune cells to the inflammatory site occurs through chemokine gradient between 4 and 6 h following allergen exposure to the conjunctival epithelium and lasts 24 h before symptom initiation [9,13]. Mast cells are crucial to the late phase response by synthesizing proinflammatory leukotrienes and prostanoids, such as LTC4 and PGD2, which then promote the production of inflammatory cytokines, such as interleukin-4, interleukin-5, interleukin-13, and interleukin-1a/b [13].

Topical mast cells stabilizers (single acting) inhibit mast cell degranulation and histamine release, reduce the recruitment of inflammatory cells, and reduce the allergic reaction cascade, thus affecting the late-phase response of allergic conjunctivitis [6]. Mast cell stabilizers have been proven as effective reducers of allergy signs and symptoms, but in recent years they are rarely used as exclusive single-acting treatment, but rather as dual-treatment with antihistamines, as a result of their slow activation (3–5 days) [8].

The classic single-action mast cell stabilizers drugs are cromolyn, nedocromil, pemirolast, and lodoxamine. These drugs inhibit the degranulation of mast cells, followed by the release of histamine [9,14].

DUAL-ACTION AGENTS

In recent years, dual-action agents which combine both topical antihistamine and mast cell-stabilizing properties were found to be the treatment of choice for mild forms of allergic conjunctivitis; SAC and PAC. The superiority of these multimodal agents over previously used antihistamines is the combined action of histamine receptor antagonists, coupled with the action of mast cell stabilizers [11]. This combination of two mechanisms rapidly affects the early, as well as the late, phase of allergic conjunctivitis signs and symptoms. A single-combined molecule of dual-acting antihistamine/mast cell stabilizers blocks the histamine receptor, regulates mast cell reaction, and suppresses the inflammatory mediators' secretions, thereby controlling allergic conjunctivitis [8]. The antihistaminic effect reduces the early phase of ocular allergic response action such as itching, whereas the stabilization of mast cell inhibits the release of inflammatory mediators such as cytokines and lipid mediators, which is associated with the late-phase response of ocular allergic conjunctivitis [15].

Some of the dual-action agents have multiple routes of action on allergic conjunctivitis. Several dual-action drugs have immunological effects, such as inhibition of eosinophil chemotaxis and activation of interleukin-5, leukotrienes and platelet-activating factor, in addition to histamine receptor inverse agonism and regulation of mast cell action [9]. The available dual-acting drugs are azelastine, ketotifen, epinastine, and olopatadine [9,14]. No sensitivity or contraindication was found for any of the formulation components of the topical dual-acting antihistamine/mast cell stabilizing agents. Rather, an increase in comfort for wearing contact lenses in a 2 h period was recorded [8].

CURENT TRENDS

Over the past 2 decades it has become known that the exclusive action of blocking the histamine release does not prevent the entire allergic response of the ocular surface, due to further release of

inflammatory mediators. Therefore, the novel treatments of AC consists of combined agents that block the histamine H1 receptors, along with mechanisms of mast cell stabilization and cytokine activity antagonism [9].

In a large cross-sectional European study, involving a cohort of 3545 patients affected by ocular allergy treated by 304 ophthalmologists, a stratification of the different treatments was made. Interestingly, the treatment paradigm was as follows: topical decongestants were used in 43% of patients, corticosteroids in 41%, antihistamines in 29%, systemic antihistamines in 27%, and mast cell stabilizers in 15% [7].

Beyond the histamine release and local inflammation, the pathophysiology of allergic reaction also includes secretion of proteolytic enzymes by the allergens that enhance degradation of tight junction proteins that disrupt the epithelial barrier function. This mechanism also involves recruitment of eosinophils via H4 receptor interaction, which destabilize the barrier function of the conjunctival epithelium. Thus, blocking the H4 receptor promotes the prevention of allergic conjunctivitis [15,16].

The alcaftadine medication inhibits the influx of eosinophils and prevents disruption of the tight junction proteins. It is a multiple action antiallergic therapeutic agent, with a mechanism of mast cell stabilizing, anti-inflammatory and inverse agonist activity on H1, H2, and H4 receptors [15]. As antagonist to H4 receptor, alcaftadine inhibits H4 receptor-mediated Th2-lymphocyte-driven allergic conjunctival response and also prevents the release of cytokines and chemokines, upregulation of adhesion molecules, and the recruitment of immune cells. Over extensive studies, including several randomized, double-blind, placebo-controlled studies, alcaftadine was considered to be a safe and effective treatment on ocular conjunctival signs and symptoms, particularly on ocular itch, redness, chemosis and eyelid swelling, and was shown to have a longer duration of action [2,4,15–17].

Antazoline, a first-generation antihistamine, has anticholinergic properties and is given together with decongestants such as naphazoline and/or tetrahydrozoline that are used for conjunctional blood vessels constriction [18], but the long-term use in such combination may lead to rebound hyperemia [9].

The preservative-free levocabastine hydrochloride ophthalmic solution was found to be appropriate for prophylactic treatment of allergic conjunctivitis, though still not available in the United States [9]. Five clinical studies comparing the antihistamine levocabastine vs. placebo and nine studies comparing the antihistamine azelastine vs. placebo, all found these drugs to be effective [14].

In a recent meta-analysis, 23 randomized controlled trials (RCTs) were analyzed to assess the safety and efficacy of the topical antiallergic conjunctivitis medication, olopatadine [19]. This conventional medication is a dual-action, selective H1-receptor antagonist and a mast cell stabilizer. On human conjunctival mast cells, it causes a reduction in the release of immunologically stimulated proinflammatory mediators, thus preventing the local inflammation in the conjunctiva [4,16]. Compared with placebo, olopatadine was found, in the mentioned meta-analysis, to be associated with a decrease in ocular itch, with a pooled-mean difference -1.33 ($P < 0.00001$) and reduction of the ocular hyperemia of -0.92 ($P < 0.00001$). Although comparing the olopatadine with other agents, the alcaftadine had higher effect on ocular itch (pooled-mean difference $= 0.39$; $P < 0.00001$), but a comparable effect was found with epinastine and ketotifen to the olopatadine [19]. The epinastine hydrochloride, a selective inverse histamine H1 receptor agonist that also inhibits IgE receptor-mediated histamine release from mast cells, was clinically explored in terms of safety and efficacy on patients with SAC. Compared with placebo, the epinastine 0.05% had superiority, but noninferiority to olopatadine 0.1% ophthalmic solution (olopatadine) for cedar pollen antigen-induced ocular itching and conjunctival hyperemia [20].

In a randomized, masked clinical trial, Bilkhu *et al*. explored whether artificial tears and cold compresses, alone or in combination, given with epinastine hydrochloride, are effective as topical antiallergic medications. Compared with no treatment, it was reported that cold compress and artificial tears had statistically significant higher effect on signs and symptoms of allergic conjunctivitis [21].

A new clinical trial compared the effectiveness and safety of topical olopatadine and ketotifen, both drugs having antihistaminic and mast cell-stabilizing properties, as treatment for allergic conjunctivitis. Overall 60 patients received olopatadine HCl 0.1% or ketotifen fumarate 0.025%, and were followed up on the 4th, 15th, and 30th days to evaluate symptoms, signs, and quality of life. A significant reduction was shown by the 4th and 15th days of olopatadine and ketotifen application in scores of itching, tearing, redness, eyelid swelling, chemosis, and papillae addition, as well as quality of life scores, comparable to the baseline ($P = 0.001$). Comparing the two medications, olopatadine significantly led to reduction in itching, tearing, hyperemia, conjunctival papillae, and total allergic conjunctivitis scores ($P = 0.001$) [22▪▪].

Carr and colleagues have recently reported on a newly developed treatment option that was

Table 1. Topical main pharmacological antihistamines and mast cell stabilizers agents in allergic conjunctivitis treatment assay

Drug class	Main available drugs	Mechanism of action
Antihistamines	Antazoline	Blockage of histamine receptors (blocking all and/or some of H1, H2, H3 and H4 receptors) Inverse histamine receptor agonists
	Pheniramine	
	Levocabastine	
	Emedastine	
	Bepotastine	
Mast cell stabilizers	Cromolyn	Inhibition of mast cells degranulation and the release of histamine
	Nedocromil	
	Pemirolast	
	Lodoxamine	
Dual-action agents	Azelastine	Antagonism to H1 receptors and prevention of mast cells degranulation
	Ketotifen	
	Epinastine	
	Olopatadine	
New formulas	Alcaftadine	Inverse agonism to H4 receptors, prevention of release of cytokines and chemokines, upregulation of adhesion molecules and the recruitment of immune cells
	Epinastine hydrochloride 0.05%	Antagonism to H1 receptors and inhibition of IgE receptor-mediated histamine release from mast cells
	Olopatadine in high concentration of 0.77%	Antagonism to H1 receptors and prevention of mast cells degranulation. Rapid action and long-standing effect of 24 h (usage: once daily)

explored in several RCTs. Dual-acting agent olopatadine with higher-concentration formulation of 0.77%, rather than the widely-used olopatadine 0.2%, had a superior efficacy in terms of ocular itching, conjunctival redness, and chemosis. Moreover, the high concentration olopatadine has shown extended duration of efficacy beyond that of the 16 h duration of olopatadine 0.2%, up to 24 h effect. In a multicenter, randomized, double-blind, controlled clinical trial that included 202 patients with allergic conjunctivitis, comparing the olopatadine 0.2–0.77%, both given once-daily, the latter preparation was shown to have better efficacy on reported symptoms of inflammation, including ocular itching and conjunctival redness, even 24 h after instillation [23].

Another study included 345 adults with a history of allergic conjunctivitis that received a single dose of olopatadine 0.77%, olopatadine 0.2%, olopatadine 0.1%, or vehicle. The reduction in ocular itch was shown in 41% of the patients who used the olopatadine 0.77%, compared with vehicle (4% of patients, $P < 0.0001$) and olopatadine 0.2% (26% of patients, $P < 0.05$) with longer duration of action and with similar safety profile to the low-dose medication [23]. These RCTs led to conclusion that the novel topical ocular antihistamine–mast cell stabilizer formulation olopatadine 0.77% significantly reduces the acute ocular signs and symptoms of allergic conjunctivitis at an onset of 24 h. Using it once-daily, this medication also has a high degree of overall efficacy and is well tolerated for chronic use. Therefore, the olopatadine 0.77% may be considered as treatment of choice in SAC or PAC cases (Table 1).

Some claim that the treatment of allergic conjunctivitis is best classified by the duration and severity of signs and symptoms, rather than 'seasonal' or 'perennial' classification [8]. In severe cases of AC, as in AKC and VKC, multidisciplinary approach is required. In such cases, the exclusive treatment by antihistamines or mast cell stabilizers alone does not provide a sufficient reduction in the severe signs and symptoms. These are treated conventionally with avoidance of allergens, topical mast cell stabilizers, antihistamines, and corticosteroids. Aggressive treatment includes tacrolimus, a strong immunosuppressant that can suppress proliferation of T-cell and B-cell proliferation, topical cyclosporin A, corticosteroids, and an amniotic membrane that has anti-inflammatory effect [6]. The tacrolimus and amniotic membrane treatments manage the long-standing severe inflammation and prevent sight-threatening corneal complications [24].

Another interesting clinical trial on nonpharmacological treatments for allergic conjunctivitis reported that sunglasses may significantly reduce ocular symptoms ($P = 0.002$) and antihistamines

usage ($P = 0.009$) in patients with allergic conjunctivitis [25].

A newly suggested algorithm for the management of allergic conjunctivitis was recently reported by Bielory and colleagues, that is based on the literature, as well as on the authors clinical experience, and stratified the treatment by three main levels of allergic conjunctivitis [8]. This algorithm provides an approach, by which the treatment of mild allergic conjunctivitis, with minimal symptomatic itching, can start with nonpharmacological alternatives, such as cold compresses and topical lubricating. An alternative to such cases can be over-the-counter medication or ocular antihistamine/mast cell stabilizers. Patients with mild to severe itching and a prolonged history of symptoms, with no significant redness, can be treated with topical ocular antihistamine/mast cell stabilizer, with steroids being frequently used in such cases. The third-level treatment is for patients with moderate to severe and long-standing itching, redness, tearing burning, and other symptoms; they should be treated with topical ocular antihistamine/mast cell stabilizer and/or a topical ocular corticosteroid, with the alternative option of immunotherapy drugs.

CONCLUSION

The main aims of the treatment and management of allergic conjunctivitis are to prevent or minimize the inflammatory cascade associated with allergic response, in the acute and late phases of the disease. The mild forms of allergic conjunctivitis, PAC, and SAC can be treated with nonpharmacological treatments, such as cold compress and artificial tears. In these cases, the conventional antihistamines or mast cell stabilizers can be prescribed. However, exclusive treatment with one of these agents is not sufficient. In past years, undoubtedly, the dual-action antihistamines/mast cell stabilizers agents became the primary treatment of choice. Ocular itch, redness, eyelid swelling, and other common symptoms are rapidly improved for long periods using those agents. The newest medications are the alcaftadine and olopatadine 0.7% formulation, demonstrating the highest effectiveness on allergic conjunctivitis with the same safety profile as other accepted medications, particularly on the most common allergic conjunctivitis subtypes, SAC and PAC. In the most severe cases, such as AKC and PKC, steroids and immunotherapy are commonly used to supplement treatment.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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