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RHINITIS, CONJUNCTIVITIS, AND SINUSITIS (JOHN J. OPPENHEIMER & JONATHAN CORREN, SECTION EDITORS)

# Emerging Therapeutics for Ocular Surface Disease

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## Abstract

**Purpose of Review** The purpose of this article is to review treatment advances in ocular allergy that include the treatment of the various signs and symptoms of the allergic inflammatory response of the ocular surface.

**Recent Findings** Recent studies have demonstrated improved pharmacological effect of topical agents with artificial tears and cold compresses; brimonidine, a new ophthalmic decongestant which has demonstrated decreased rebound conjunctivitis; and potential use of contact lens and other novel delivery instruments to increase medication retention time.

**Summary** Currently, there have been limited advances in novel ophthalmic treatments. Non-pharmacological interventions have demonstrated in a randomized control study that artificial tears and the use cold compresses alone or in combination with ophthalmic antihistamines can enhance the effectiveness of a traditional pharmacological therapy. The primary advances have been the start of head-to-head studies comparing various agents actively being used in the treatment of ocular allergy. In addition, there has been increasing interest in the development of novel delivery systems to increase residence time of pharmacological agents in the ocular surface such as nanoparticles, microfilms; examining novel pathways of controlling the allergic inflammatory response of the ocular surface such as modulation of cytokines, transcription factors, and immunophilins.

**Keywords** Ocular surface disease · Ophthalmic decongestant · Ocular allergy · Conjunctivitis · Allergic inflammation · Allergic conjunctivitis · Pharmacotherapy · Contact lenses · Non-pharmacological treatments · Lubrication

## Introduction

The conjunctiva of the ocular anterior surface is one of the most commonly involved target organs for the allergic inflammatory response [1] that affects 15–20% of the population [2, 3]. Ocular allergy occurs through the activation of Th2 cell–mediated cascade leading to a predominant development of IgE or in combination with T lymphocyte–mediated disorder and the subsequent development of acute and chronic forms of ocular allergy. This proinflammatory state through the activation of transcription factors creates a cascade immune effect via increased cellular infiltration (e.g., eosinophils), secretion of chemokines, cytokines, and metalloproteinases, that further promote ocular surface damage and disruption of epithelial barriers.

This article is part of the Topical Collection on *Rhinitis*, *Conjunctivitis*, *and Sinusitis*

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## Background

### Allergic Conjunctivitis

Allergic conjunctivitis (AC) represents a spectrum of conditions ranging from acute to chronic forms. The acute forms include seasonal allergic conjunctivitis (SAC), the most common form triggered by outdoor allergens, and perennial conjunctivitis (PAC), a variant of AC because of continuous exposure to indoor allergens such as dust mite and animal dander [3]. The chronic conditions include vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC) [3]. Many also call the effect of

preservatives on the ocular surface an "allergic" response. Current treatments of AC include the use of antiallergic eye drops for mild forms, while recurrences of ocular surface inflammation with corneal involvement in severe forms require the use of topical steroids to avoid visual impairment (see Table 1). Novel steroid sparing therapies such as immunophilins (e.g., Cyclosporine A, Tacrolimus) have been proposed to treat acute and chronic forms of ocular allergy [4]. The treatment commonly involves a stepwise approach [5] from non-pharmacological treatments to common anti-allergy therapies and immunomodulatory treatments for the more chronic forms.

## Treatment of Allergic Conjunctivitis

### Non-pharmacologic

#### Cold Compresses

Cold compresses are commonly known to provide considerable symptomatic relief, especially from ocular pruritus. In an interesting study of grass-pollen allergic patients ($n = 18$ mean age, $29.5 \pm 11.0$ years) using an environmental chamber, the impact of artificial tears and cold compress alone or in combination was investigated if it could provide a treatment benefit or could enhance the use of a topical antiallergic medication. Signs and symptoms were measured at baseline and every 10 min after treatment for up to 1 h. One of the unique outcomes was that lubrication with artificial tears and cold compresses demonstrated a therapeutic effect on the signs and symptoms of allergic conjunctivitis [6••] (see Tables 2 and 3). This has led to the common request that patients refrigerate all ocular medications to provide additional subjective relief when immediately applied in a cold state.

#### 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 2–6 times a day as necessary. This primarily assists in the direct removal and dilution of allergens that may come in contact with the ocular surface. Ocular lubricants also vary by class, osmolarity, and electrolyte composition with no head-to-head studies providing any guidance as to a clear favorite. Of interest, is that lubrication in addition to cold compresses did provide significant relief, but clearly, the addition of the ophthalmic antihistamine epinastine provided the most reduction in the signs and symptoms associated with allergic conjunctivitis [6••].

### Pharmacologic

#### Decongestants

Redness (conjunctival injection/erythema) is one of the most common complaints from which many prescription medications have sought to achieve clinical relief while also providing control of ocular pruritus—the ocular "itch." Topical decongestants are the primary treatment being highly selective in reducing redness through non-selective mixed alpha-1-adrenergic and vasoconstrictive derivatives of imidazolines such as phenylephrine, tetrahydrozoline (e.g., Visine™ and others in the USA), naphazoline (Clear Eyes™ and others in the USA), and oxymetazoline (Visine L.R.™). Vasoconstrictors are widely used in combination with topical antihistamines such as naphazoline and pheniramine (Naphcon-A) [7] to provide the targeted relief of red and itch affecting the ocular surface. Major drawbacks of the commonly used vasoconstrictor/decongestant agents include conjunctivitis medicamentosa, the development of rebound redness reported with discontinuation, and the loss of effectiveness or tolerance over time—tachyphylaxis [8]. However, brimonidine demonstrated statistically significant improvement of redness with minimally observed rebound phenomena when given four times daily over a 4-week course in recent randomized clinical trials [9••, 10].

#### Contact Lenses

In the realm of advice given to patients that use specific medications or prescriptions, the primary intervention may actually be the use of contact lenses as a barrier (band-aid)—such as in the treatment of keratoconus or Stevens Johnson Syndrome [11]. However, the overall goal of "pharmacotherapeutic" interventions involves interfering with inflammatory mediators that underlie the development of the various signs and symptoms of ocular allergy [12]. However, even though currently available antiallergic medications are compatible with the use of contact lenses, it is the general recommendation that either the medication be placed prior to the use of eye drops or the lenses be removed prior to the ophthalmic application. This is due to the potential for interactions between lenses and ophthalmic preservatives, a concern that has typically led to the exclusion of contact lenses from clinical studies of ophthalmic allergy agents. Thus, regulatory agencies have recommended that ophthalmic agents should not be used while wearing lenses due to the lack of compatibility data.

There have been recent developments in the combination of contact lenses plus medications with specific focus on the

**Table 1** Therapeutic interventions for AC

| Therapeutic intervention | Clinical rationale | Pharmaceutical agents | Comments |
|---|---|---|---|
| Cold compresses | • Decrease nerve C fiber stimulation<br>• Reduce superficial vasodilation | | • More effective than drug in reducing ocular surface temperature<br>• Cold compress + artificial tears is more effective than drug in reducing hyperemia |
| Preservative-free tears | • Lavage<br>• Dilutional effect | • Artificial tears | • Extremely soothing<br>• Recommend refrigeration to improve symptomatic relief<br>• Inexpensive OTC<br>• Use as needed<br>• Effective at washing away allergen<br>• Barrier to further exposure of allergens<br>• Can be more efficacious than antihistamines in reducing hyperemia and ocular surface temperature |
| Topical antihistamine and decongestants | • Antihistamine relieves pruritus<br>• Vasoconstrictor relieves injection | • Antazoline-naphazoline<br>• Pheniramine-naphazoline<br>• Antazoline-tetryzoline | • Quick onset<br>• More effective than systemic antihistamines<br>• Limited duration of action<br>• Frequent dosing required |
| Topical antihistamine and mast cell stabilizer | • Single agent with dual action<br>• Has immediate and prophylactic activity<br>• Eliminates need for 2-drug therapy<br>• Comfort enhances patient compliance | • Olopatadine<br>• Ketotifen<br>• Azelastine<br>• Epinastine | • BID dosing<br>• Dual acting agents<br>• Antihistamine, mast cell stabilizer, inhibitor of inflammatory mediators<br>• More effective at relieving symptoms than other classes of agents<br>• Longer duration of action<br>• Safe and effective for 3 years and older |
| Topical mast cell stabilizers | • Safe and effective for allergic diseases affecting corneal changes | • Cromolyn<br>• Lodoxamide<br>• Nedocromil<br>• Pemirolast | • Cromolyn relives mild-to-moderate symptoms of vernal keratoconjunctivitis, vernal conjunctivitis, vernal keratitis<br>• Lodoxamide is highly potent |
| Topical H1-antihistamines | • Relieves signs and symptoms of pruritus and erythema | • Levocabastine<br>• Emedastine<br>• Bepotastine<br>• Alcaftadine<br>• Cetirizine<br>• Azelastine*<br>• Epinastine*<br>• Ketotifen*<br>• Olopatadine* | • Dosing 1–4 times daily<br>• Safe and effective for 3 years and older |
| Topical NSAIDs | • Relieves pruritus | • Ketorolac | • Stinging and/or burning on instillation experienced up to 40% of patients |
| Decongestants | • Counteract histamine-induced erythema<br>• Vasoconstrictive properties | • Oxymetazoline<br>• Phenylephrine<br>• Tetrahydrozoline<br>• Naphazoline<br>• Brimonidine | • Brimonidine reduces chance of rebound symptoms<br>• Often overused by patients<br>• Loss of efficacy and eye irritation common with use<br>• Contraindication with narrow-angle glaucoma<br>• OTC |
| Topical corticosteroids | • Relieves all facets of the inflammatory response including erythema, edema and pruritus | • Loteprednol<br>• Rimexolone<br>• Fluorometholone<br>• Dexamethasone<br>• Prednisolone | • Appropriate for short term use only<br>• Contraindicated in patients with viral infections |

*Have demonstrated both mast cell stabilizer and antihistamine properties

use of antihistamines. The goal is to provide the contact lens–wearing population with the opportunity to use contact lenses for vision correction regardless of their sensitivity to seasonal and perennial allergen exposure. Studies have recently demonstrated that medication-impregnated contact lenses generate a trap in the post-lens tear film that extend the duration of exposure to medication from 90 s to at least 30 min [13••]. Therefore, contact lens–based drug delivery systems

**Table 2** Pharmacological vs non-pharmacological treatments

| Treatment | | Drug + CC vs | CC vs | AT vs | AT + CC vs | Vehicle vs |
|---|---|---|---|---|---|---|
| Drug | Hyperemia | +* | + | + | + | − |
| Drug + CC | Hyperemia | | − | − | + | − |
| CC | Hyperemia | | | = | + | − |
| AT | Hyperemia | | | | + | − |
| AT + CC | Hyperemia | | | | | − |

* Hyperemia in the temporal portion of the ocular surface was found to be statistically significant

*CC* cold compresses, *AT* artificial tears

Vehicle, placebo; drug, epinastine HCL; +, more effective at decreasing hyperemia; −, less effective at decreasing hyperemia; =, comparable effectiveness

Conjunctival redness (hyperemia) of the bulbar surface and ocular symptoms decreased with non-pharmaceutical treatments compared with no treatment ($p < 0.05$)

Artificial tears combined with CC reduced redness more than other treatments ($p < 0.05$)

The treatment effect of EH was enhanced when combine with a CC ($p < 0.001$)

At all measurement intervals, symptoms were reduced for both EH and EH combined with CC than CC or ATs alone or in combination ($p < 0.014$)

for therapeutic delivery of anti-allergy medications that include ketotifen and olopatadine are underway [14–16] (Clintrials.gov numbers NCT00445874 and NCT00432757).

## Antihistamines

Oral antihistamines have classically been the cornerstone of treatment for "rhinoconjunctivitis"; however, these agents have anticholinergic activity that can cause and/or exacerbate tear film dysfunction that commonly exists in patients with ocular allergy. This has led to the preference of using topical antihistamines or multiple action agents. Several of the oral antihistamines have been developed as ophthalmic preparations, e.g., ketotifen, cetirizine, and bilastine. Bilastine is presently undergoing a phase 2 dosing study to evaluate its efficacy in varying concentrations (0.2%, 0.4%, 0.6%) (NCT03231969) and has subsequently entered clinical trials in a phase 3 study comparing bilastine 0.6% to a vehicle and ketotifen 0.025% (NCT03479307). Cetirizine is a potent second-generation antihistamine that has been reformulated into an ophthalmic preparation (AC-170 0.24%) for the treatment of ocular allergies. It has undergone pharmacology, single center, and several multicenter studies (NCT01551056; NCT02756624; NCT01685242; NNCT01881113; NCT02132169) with positive results in decreasing ocular pruritus, but not redness, leading to US FDA regulatory approval in 2018.

**Head-to-Head Ocular Allergy Studies** Head-to-head studies started to appear in the literature in the 1990s but were extremely rare as pharmaceutical companies were concerned with inferiority. But with a decrease of novel compounds, the number of head-to-head comparative studies has increased to identify potential advantages of one therapy over another. These studies have been confusing as poorly designed studies compare topical agent effects with the acute and chronic phases of the allergic inflammatory response (e.g., finding an ophthalmic steroid or non-steroidal drug being inferior to an antihistamine in the treatment of the acute phase). Although

**Table 3** Pharmacological vs non-pharmacological treatments

| Treatment | | Drug + CC vs | CC vs | AT vs | AT + CC vs | Vehicle vs |
|---|---|---|---|---|---|---|
| Drug | Temperature | + | + | − | + | = |
| Drug + CC | Temperature | | = | − | = | − |
| CC | Temperature | | | − | + | − |
| AT | Temperature | | | | + | = |
| AT + CC | Temperature | | | | | − |

*CC* cold compress, *AT* artificial tears

Vehicle, placebo; drug, epinastine HCL; +, more effective at decreasing ocular temp; −, less effective at decreasing ocular temp; =, comparable effectiveness

Conjunctival temperature recovered to baseline faster with non-pharmaceutical treatments compared with no treatment ($p < 0.05$)

Topical application of an ophthalmic antihistamine was enhanced by combining it with a CC ($p < 0.001$)

**Table 4** Head-to-head studies

| | Olopatadine vs | Lodoxamide vs | Emedastine vs | Fluorometholone vs |
|---|---|---|---|---|
| Epinastine | ≥R<br>≥OI | | =SS | <SS |
| Alcaftadine | <OI | | | |
| Ketotifen | ≥OI<br>≥R | | =SS | <SS |
| Loteprednol | >OI<br>>R | | | |
| Emedastine | =SS | | | <SS |
| Levocabastine | | | >OI<br>>R | |
| Olopatadine | 0.77% > 0.2%<br>OI | | | <SS |
| Cromolyn | >OI<br>>R | >CD4(+)<br>>CD23(+)<br>>QR | | |
| Ketorolac | >OI | | | >R<br>=OI |
| Bepotastine | <OI | | | |

>, reduced symptoms more effectively; <, reduced symptoms less effectively; =, no difference in effectiveness

*OI* ocular itch, *R* redness, *QR* quicker relief, *SS* signs and symptoms

there are no clear leaders, there are trends to be noted (see Table 4) [17–35].

## Immunophilins

Topical calcineurin inhibitors known as the immunophilins have gone from experimental to clinical uses with the recent approval of this group of agents for the treatment of chronic forms of allergic conjunctivitis that include vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis [36]. Studies on seasonal allergic conjunctivitis have failed but appear to have a major role in the treatment of the chronic forms of ocular allergy including AKC and VKC. Multiple studies have highlighted the promising effects of tacrolimus with significant reductions in symptom score severity (approaching 50%) [37–44].

### Corticosteroids

**Steroid Alternatives** Given the potency and potentially devastating side effect profile of many of the corticosteroids, a new class of drugs known as Selective Glucocorticoid Receptor Agonists (SEGRA) has been developed. SEGRAs are being investigated as an alternative "steroid sparing agent" that maintain the anti-inflammatory activity of steroids, but with reduced side effects. ZK209614, a recently identified novel SEGRA, exerts strong transrepression and weak transactivation that displays high binding affinity to the glucocorticoid receptor with promising anti-inflammatory and antiallergic action in animal models of conjunctivitis [45] and has demonstrated being slightly less efficacious than dexamethasone in the AC model [45]. Mapracorat is a SEGRA undergoing evaluation for treatment of anterior surface disorders of the eye that include allergic conjunctivitis and dry eye syndrome as well as inflammation following cataract surgery.

In both a carrageenan-induced conjunctivitis model and allergic conjunctivitis model in rats when given ZK209614 and betamethasone phosphate as eyedrops, each had an inhibitory effect on edema with the reduction of vascular permeability at a concentration of 0.1% and demonstrated no increase in intraocular pressure when compared to topically administered betamethasone phosphate. Another SEGRA, AZD9567, is presently undergoing phase 1 studies for safety, tolerability, pharmacokinetics, and effects on glucose homeostasis (pharmacodynamics) in comparison to prednisolone 60 mg and placebo (NCT02512575) [46].

**SEGRA** In support of studies done on mapracorat, several animal studies were conducted.

In guinea pigs, mapracorat was effective in reducing clinical signs, eosinophil infiltration, and eosinophil peroxidase activity in the guinea pig conjunctiva; furthermore, it reduced conjunctival mRNA levels and protein expression of both CCL5 and CCL11 [47]. In normotensive rabbits, mapracorat has proven to have a more favorable effect on IOP than dexamethasone while maintaining a comparable anti-inflammatory profile [48]. Additionally, in experimental models of ocular diseases, mapracorat

reduced clinical symptoms, eosinophil recruitment, chemokines, and proinflammatory cytokine production at ocular level, which proves that it acts at preventing early and late phases of allergic response. Mapracorat also induced a lower increase of intraocular pressure compared to dexamethasone [49].

## Immunobiologicals

### Anti-IgE

Anti-IgE (Omalizumab), a recombinant anti-IgE mAb, has been considered as a potential treatment for severe ocular allergies. Studies are limited to case reports involving AKC and VKC patients (pediatric and adult) [50–56], treatment with omalizumab ranged with effects noted from the first dose, and further improvement with longer treatment up to 2 years. Reportedly, decreased ocular symptoms of burning and/or itching and overall need for topical antihistamines, with improved physical exam findings (i.e., decreased erythema, cobblestone papillae), were noted after 2 months.

### Cytokine Antagonists

#### IL-5

The eosinophil differentiation factor, IL-5, is the focus of several therapeutic treatments approved by the Food and Drug Administration that include mepolizumab (GlaxoSmithKline, Research Triangle Park, North Carolina, USA) and reslizumab (formerly SCH55700, Cinquil; Teva Pharmaceuticals, Petah Tikva, Israel) [57]. There have been no clinical trials for the treatment of eosinophilic ocular disorders, but there have reports of some adverse effects with increased conjunctival irritation from the use of duplimumab (Dupixent). Duplimumab is approved for the treatment of atopic dermatitis due to its inhibition of interleukin 4 (IL-4)) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Adverse reports of conjunctivitis have been reported in the treatment of atopic dermatitis, but not in the specific studies related to asthma. The mechanism of this adverse effect is unknown.

#### Interleukin-1/Interferon

In an early study to appreciate the potential impact of IL-1 in allergic conjunctivitis, the IL-1 receptor antagonist-IL-1Ra demonstrated its potential impact in suppressing allergic eye disease by a down-modulation of the recruitment of eosinophils and other inflammatory cells (Keane-Myers, Miyazaki et al. 1999). EBI-005 is a novel protein chimera of IL-1β and IL-1 receptor antagonist (IL-1Ra or anakinra) that potently binds IL-1R1 and blocks signaling (Kovalchin, King et al. 2018). The major thrust of this product has been on dry eye disease, but has also shown promise in decreasing the impact of the late phase of the allergic response. EBI-005 has completed phase 2 clinical trials in a randomized, double-masked, vehicle-controlled study using thrice-a-day dosing in an environmental exposure chamber (EEC) and the other was with a conjunctival allergen challenge (CAC). The primary endpoint of itching in the EEC group was not met, but in the CAC, there was a statistically significant decrease in itching ($p = 0.033$), tearing ($p = 0.004$), and nasal symptoms ($p = 0.0004$) (Goldstein, Tubridy et al. 2015). Interferon alpha-2b has appeared to be safe and effective in a limited study in the treatment of recalcitrant VKC [43].

## Concepts and Models of Future Allergic Conjunctivitis Prospects

### Microfilm Carrier

PLCL (D,L-lactide-co-epsilon-caprolactone) is a microfilm that was studied with tacrolimus in a mouse allergic conjunctivitis model comparing it to dexamethasone, tacrolimus, and tacrolimus + dexamethasone eye drops. The tacrolimus microfilm delivery system was able to deliver a clinically sufficient dose with a steady rate of 0.212 to 0.243 μg/day in vivo. Promising results for all groups treated with tacrolimus showed a statistically significant reduction in the allergic clinical scores throughout the study period at 4 weeks after treatment. Histopathologic and immunohistochemical staining with CD11c, CD4, and IL-4 were also performed and demonstrated suppressed eosinophils and the CD marker expression with the most reduction noted in the dexamethasone combined with tacrolimus [39].

### Nanoparticles

A study was conducted to create and improve an ophthalmic delivery of ketotifen in which a nanoparticle formulation was developed in an attempt to reduce the frequency of administration and to obtain controlled release to improve the drug delivery. The polymer Eudragit RL 100 was used with ketotifen that permitted the release from the various formulations after 24 h from 65 to 88%. Nanoparticles containing the higher polymer concentration (1:15) resulted in a faster drug release and a higher drug penetration while the nanoparticles containing a lower polymer concentration (1:7.5) provided a more sustained release of the drug and thus a slower permeation through the cornea [58, 59••].

### Cutaneous Photoreceptors

Noting that the ocular mucosa is a cutaneous connective tissue and that exposure to UV radiation induces a local immune suppression has been linked to skin cancer via an epidermal photoreceptor that is converted into a biologically recognizable signal through two photoreceptors: DNA and *trans*-urocanic acid (UCA). It has been reported that the potential modulation of *cis*-UCA may be a potential target for cutaneous disorders associated with IgE-mediated mast cell degranulation [60]. *Trans*-UCA is normally found in the outermost layer of skin and isomerizes to the cis isomer upon exposure to UV radiation. Cis-UCA has been studied in two experimental models of allergic conjunctivitis mediated by the mast cell degranulator C48/80 and the ovalbumin model. Comparing mixtures of Cis-UCU with dexamethasone, ketotifen and olopatadine demonstrated that cis-UCA 2.5% appeared to be equally effective to olopatadine in controlling allergic vascular leakage response and has some anti-inflammatory effect [61]. While earlier forays into human studies in a phase 1, double-blinded, placebo-controlled study demonstrated the safety, ocular tolerability, and pharmacokinetics of 0.5% and 2.5% cis-urocanic acid (cis-UCA) eye drops [62].

### Adhesion Molecule

The adhesion molecule, α4β1 integrin, is expressed in eosinophils interacting with the vascular cell adhesion molecule-1 (VCAM-1) and fibronectin in vascular endothelial cells promoting eosinophil activation and infiltration in allergic conjunctivitis. A novel α4 integrin antagonist, DS-70, was studied in animal models of allergic conjunctivitis using ovalbumin-sensitized guinea pigs. DS-70 bound to α4 β1 integrin with nanomolar affinity thus preventing the adhesion of α4 integrin–expressing cells antagonizing VCAM-1-mediated degranulation of mast cells and eosinophils and ERK 1/2 phosphorylation. Interestingly, DS-70 was minimally degraded (~20%) after an 8-h incubation with serum and demonstrated a dose-dependently reduction of the clinical symptoms of allergic conjunctivitis, conjunctival α4 integrin expression, and conjunctival levels of chemokines and cytokines in ovalbumin-sensitized guinea pigs [63].

### Transcription Factors

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls cytokine production and cell survival. In a murine model of allergic conjunctivitis, nuclear factor–κB activation by the common ophthalmic preservative benzalkonium chloride that induces conjunctival inflammation was reversed by topical NF-κB inhibitors. This suggests a new pharmacological target for preservative toxicity and highlights the importance of conjunctival tolerance in ocular surface homeostasis [64].

### Cell Wall Components

β-1,3-Glucan (BG), a cell wall component of a variety of fungi, yeasts, and bacteria, has been studied in ovalbumin-sensitized animal models. These studies have demonstrated that BG is capable of stimulating IL-10-producing CD4+ T cells and suppressing both the Th2 response and conjunctival eosinophil infiltration in the conjunctivitis models [65].

### TRP Antagonists

Transient receptor potential (TRPV) cation channel, best known as a sensor for environmental irritants which is activated by a large number of noxious chemicals found in many plants, food, cosmetics, and pollutants, promotes the somatosensory modalities such as pain, cold and itch. TRPV1 are found on nociceptive primary afferent C-fibers in humans that are commonly involved in itch. In an animal study of ovalbumin-sensitized mice that were given a TRPA1 antagonist or TRPV1 antagonist before a topical allergen challenge, TRPV1 antagonist attenuated the clinical allergic signs of the conjunctival surface [66].

## Conclusion

There have been limited approved therapeutic options in the treatment of allergic conjunctivitis. Of interest, in the realm of non-pharmacological interventions, there has been confirmation that artificial tears and the use cold compresses alone or in combination can provide patients with a significant treatment benefit. Additionally, they have also been shown to enhance the effectiveness of a traditional pharmacological therapy. In the area of pharmacotherapy, there has been one new approval of an antihistamine, cetirizine, that has transitioned from an oral to an ophthalmic agent. There has been active research in assessing novel interventions including pursuing the selective glucocorticoid agonists that provide the anti-inflammatory component without the adverse effects, a decongestant (brimonidine) with a decreased profile of developing rebound conjunctivitis, cytokine antagonists to interfere with the allergic inflammatory cascade, and immunomodulatory agents acting as steroid sparing, and novel research into other potential antiallergic agents and novel drug delivery mechanisms.

## Expert Opinion

Allergists and other health care specialists involved in treating ocular allergy patients can now begin to appreciate the impact

of ophthalmic agents in head-to-head studies. All of these agents provide improved relief when used in conjunction with artificial tears and cold compresses. Instead of cold compresses, one should always consider refrigeration of any agent applied to the ocular surface of the eye. The future does hold improved treatment as increased retention times for medications will provide improved relief with less medication due to increased retention time on the ocular surface.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflicts of interest pertaining to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of major importance
- •• Of major importance


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