

EXPERT OPINION

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Advances in pharmacotherapy for allergic conjunctivitis

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Introduction: Allergy is the fifth leading group of chronic diseases, affecting as much as 40% of the first-world population. Its pathophysiology has a genetic component, and is driven by the immune system's sensitized response to antigens and environmental factors. As research continues to uncover the mediators responsible for ocular allergy, the development of novel drugs should progress.

Areas covered: A literature review of allergic conjunctivitis, ocular allergy and their treatment was performed using PubMed and Medline. Additional information is also included from clinicaltrials.gov and associated web sites for drugs currently in clinical trials.

Expert opinion: The initial step of therapy remains identification and avoidance of allergic triggers. The mainstay of treatment is the new generation of dual-acting antihistamines. Drugs that improve the magnitude and duration of relief, with greater subject responder rates, are gradually making their way into the clinic. Allergic conjunctivitis is a relatively easy disease to study because of the availability of models such as the conjunctival allergen challenge. New classes of drugs that target inflammatory pathways or mediators involved in the early and late-phase allergic response are being screened in these models and we are making progress in identifying the next generation of anti-allergic therapy.

Keywords: allergic conjunctivitis, antihistamine, mast cell stabilizer, ocular allergy

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1. Introduction

Allergic conjunctivitis is a common and potentially debilitating condition affecting the conjunctiva, eyelids and cornea, and it is often associated with nonocular symptoms and signs of rhinitis or sinusitis. Allergy is described as the fifth leading group of chronic diseases, affecting 50 million Americans. The Third National Health and Nutrition Examination Survey recently revealed that 40% of this American test population reported having episodes of ocular allergy [1]. The great majority of ocular allergic disease is seasonal allergic conjunctivitis (SAC), followed by perennial allergic conjunctivitis (PAC), with a very small segment of the population affected by vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) [2]. The symptoms and signs of ocular allergy are the end result of many factors, including genetics, environmental factors, ocular microbial flora and immune regulation [3]. Goals of treatment include reduction of signs, symptoms and sequelae, including redness, itching, tearing, blurry vision, conjunctival edema or chemosis, and eyelid edema.

The eyebrows, eyelids and eyelashes serve as obstacles to allergens, and a healthy tear film also helps to remove allergens from the ocular surface. Problems with any of these natural barriers may exacerbate allergic conjunctivitis. Nonpharmacologic therapy involves facilitating this barrier function, as well as avoiding antigen exposure – a difficult task when panseasonal, nearly ubiquitous allergens are the

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Article highlights.

- Allergy affects as much as 40% of the first-world population, and is described as the fifth leading group of chronic diseases.
- Its pathophysiology involves at its inception the initial sensitization to antigen, followed by early-phase activation of mast cells, with release of histamine, tryptase and activation of the arachidonic acid-cascade of prostaglandin and leukotriene synthesis. Subsequently, late-phase activation of eosinophils, basophils, T cells, macrophages and neutrophils contributes to a global chronic inflammatory state.
- Historically, treatment of ocular allergy was limited to ocular decongestants and ocular antihistamine-decongestant combinations that were of limited duration of action.
- Mast cell stabilizers have undergone continuing evolution, from cromolyn sodium to lodoxamide, nedocromil, to newer molecules such as pemirolast.
- Corticosteroids and immunomodulating agents such as cyclosporine are used for the more serious and proliferative forms of ocular allergy such as vernal and atopic keratoconjunctivitis; however, refractive seasonal allergic conjunctivitis can be treated with short-term cycles of corticosteroid therapy with careful monitoring.
- Some classes, such as non-steroidal anti-inflammatory agents and systemic antihistamines, are largely ineffective for ocular allergy.
- The dual-acting agents designed to inhibit the histamine receptor as well as stabilize the mast cell are the latest generation of ocular anti-allergic therapy. These continue to evolve in terms of duration and efficacy against itching, the primary symptom.
- Future therapies that are being evaluated with varying success include allergen desensitization immunotherapy, selective glucocorticoid receptor agonists, Toll-like receptor modulators, and Syk and JAK kinase inhibitors.

This box summarizes key points contained in the article.

cause of the allergy. Artificial tears, lubricant eye drops and eyewash are thus an important conservative treatment modality. Their use results in dilution of the antigen burden and soothing of the ocular surface. This may be an adequate non-pharmacological option in mild ocular allergy. However, conservative therapy is often not sufficient for symptomatic relief. Several classes of pharmacologic compounds have been evaluated for the treatment of ocular allergy with varying success: topical ocular decongestants, antihistamines, mast cell stabilizers, NSAIDs, dual-acting agents, conventional and last-generation corticosteroids, systemic antihistamines, and immunomodulatory therapy (Table 1) [2-5]. Several other types of molecules are under development, and target various immunological and inflammatory pathways.

2. Immune response

Once sensitization to an antigen has occurred, antigen exposure results in an early and late-phase immune response.

The early-phase reaction involves mast cell degranulation and release of histamine, prostaglandins, tryptases and leukotrienes after IgE bound to the mast cell surface is exposed to the sensitized antigen [2-4]. This process occurs within seconds to minutes (Figure 1). The late-phase reaction involves eosinophils, basophils, T cells, macrophages and neutrophils infiltrating into the conjunctiva 6 – 72 h after exposure to the allergen (Figure 2). SAC and PAC result when mast cell-bound IgE is exposed to sensitized allergens, triggering a type I hypersensitivity response. VKC and AKC result from a combination of a Type I hypersensitivity response and a Type IV hypersensitivity response, which is T-cell mediated [2-4].

Mast cells, conjunctival and corneal epithelial cells, and fibroblasts have also been shown to be involved in the late-phase response and probably contribute to recruitment of other leukocytes [3-5]. Conjunctival epithelial cells have been shown to play a key role in multiple ways. They both produce and have receptors for inflammatory cytokines and may help regulate inflammation at the ocular surface [3-5]. A recent study has also shown that conjunctival goblet cells have receptors for some of these mediators and increase mucin production during the allergic response [3-5]. Fibroblasts may be induced to produce pro-inflammatory chemokines and adhesion molecules that can contribute to the development of corneal lesions in chronic ocular allergy [4]. MMPs and tissue inhibitors of MMP have been shown to be altered in VKC, leading to excessive extracellular matrix deposition and the development of giant papillae [4]. The receptors and producers of inflammatory mediators, including histamine, cytokines, leukotrienes and prostaglandins are all potential targets for drug therapy.

3. Pharmacologic therapy (Table 1)

3.1 Ocular decongestants

In 1971, the first topical medication approved for the treatment of ocular allergy by the United States FDA was, surprisingly, the vasoconstrictor naphazoline. While α -adrenergic agonists continue to be available today in single-active, over-the-counter (OTC) products for relief of hyperemia, only in conjunction with topical antihistamines has their efficacy been established for ocular allergy [2,6]. α -Adrenergic agonists mainly target α -1 receptors for immediate-onset vasoconstriction of the conjunctival vessels, resulting in whitening and decongestion of the eye. Studies have shown that chronic use of topical α -1 adrenergic agonists can result in downregulation of α -1 adrenergic receptors causing tachyphylaxis and rebound hyperemia after they are discontinued [7]. The use of these agents should also be limited in patients with narrow angle glaucoma and angle closure glaucoma [2,8].

Low-dose brimonidine is a longer-acting α -2 agonist formulated in a much lower concentration than that approved for the treatment of glaucoma, and it is in its final stages of

Table 1. Topical anti-inflammatory or anti-allergic agents approved for ophthalmic use and evaluated for efficacy in treatment of ocular allergy.

Drug class	Agents	Mechanism of action	Common or significant side effects	Comment
Topical ocular decongestants	Naphazoline Tetrahydrozoline Phenylephrine Ephedrine Brimonidine	α -adrenergic agonists (mainly α -1 receptors)	Rebound hyperemia, conjunctivitis medicamentosa, follicular reaction, contraindicated in narrow angle glaucoma	Available alone for ocular redness or in conjunction with first generation antihistamine in over-the-counter preparations; only last 2 – 4 h; brimonidine is only α -2 agonist soon to be filed with FDA for redness approval only
Topical non-steroidal anti-inflammatory agents	Ketorolac Flurbiprofen Indomethacin Diclofenac Nevanac	Inhibition of COX-1 and COX-2 resulting in inhibition of prostaglandins	Burning sensation, itching, corneal melt	Approved only for post-operative inflammation; not shown to be effective in many failed clinical trials in PAC and SAC
Topical antihistamines	Antazoline Pheniramine Levocabastine Emedastine	Competitive blockage of histamine receptors (all block H1, and some block H2, H3, and/or H4)	Sedation, irritation, dry eye	The first two are in over-the-counter preparations with vasoconstrictors; levocabastine only available in Europe; emedastine not promoted in US
Topical mast cell stabilizers	Cromolyn Nedocromil sodium Pemirolast Lodoxamide	Inhibition of mast cell degranulation and release of histamine	Headache, burning sensation	This class taken over by dual-acting drugs Discovery of mast cell heterogeneity abdicated relevance of most of these in the eye; Cromolyn proven not active in human conjunctival mast cells; very weak activity; lodoxamide perhaps most effective in VKC
Topical dual-acting agents	Ketotifen Azelastine Epinastine Bepotastine Olopatadine Alcaftadine	Blockage of H1 receptors and inhibits mast cell degranulation and histamine release	Headache, hyperemia, burning sensation, bitter taste, dry eye	Most are approved for twice-daily dosing; CAC trials are gold standard for their approval and comparative testing; Olopatadine and alcaftadine approved for once-daily dosing Alcaftadine shown to be superior for ocular itching by numerous parameters
Topical corticosteroids	Clobetasol Dexamethasone Fluoromethalone Hydrocortisone Prednisolone Rimexolone Triamcinolone Lotoprednol	Inhibition of phospholipase A resulting in inhibition of prostaglandins and leukotriene synthesis	Increased intraocular pressure, cataract formation, delayed wound healing, headache, pharyngitis, rhinitis	Must be used with extreme caution; only for pulse therapy in chronic forms of allergy (VKC, AKC, etc.)
Topical immunomodulatory therapy	Cyclosporine A	Inhibition of T-cell activation	Irritation, burning sensation	Only approved for use in dry eye; off-label testing for chronic forms of allergy like VKC

AKC: Atopic keratoconjunctivitis; CAC: Conjunctival allergen challenge; PAC: Perennial allergic conjunctivitis; SAC: Seasonal allergic conjunctivitis; VKC: Vernal keratoconjunctivitis.

development for the treatment of ocular redness (<https://clinicaltrials.gov/ct2/show/NCT01959230?term=brimonidine+ocular+redness&rank=1>). α -2 agonists such as brimonidine have the advantage over α -1 agonists of minimum tachyphylaxis and rebound redness [9].

3.2 Antihistamines and combination antihistamine-decongestants

Systemic antihistamines have been found to be of limited efficacy in allergic conjunctivitis and may cause drying of the ocular surface, so their use should be avoided in patients

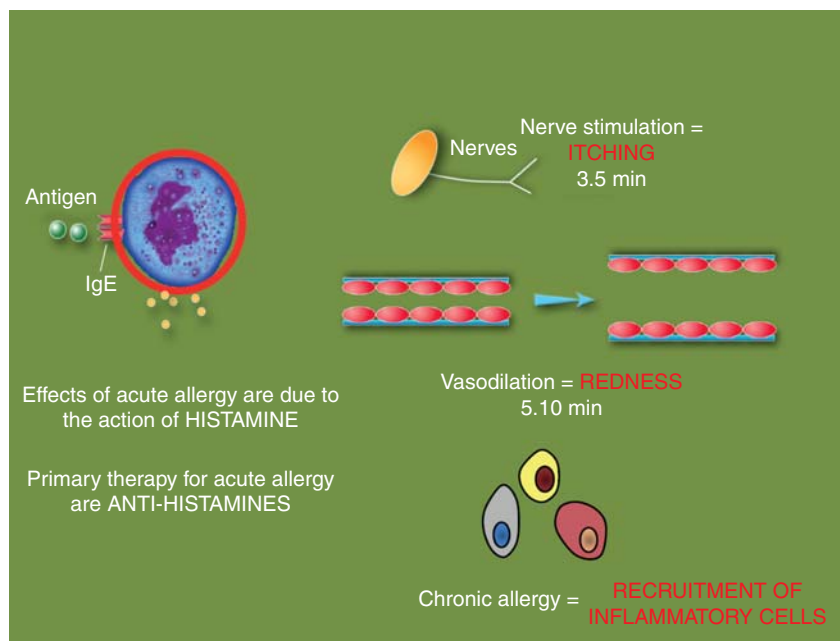


Figure 1. Treating allergy in the eye.

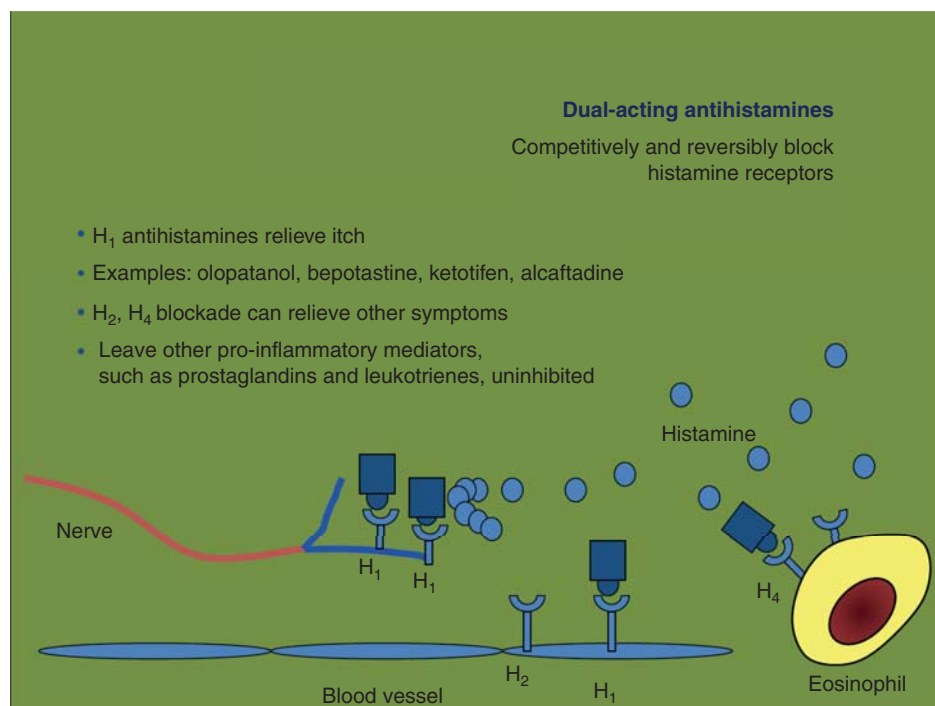


Figure 2. Dual-acting antihistamines are the latest generation of ocular anti-allergic agents.

without concurrent rhinitis or sinusitis [10]. However, histamine receptors are primary topical drug targets in ocular allergy as histamine signaling is largely responsible for signs and symptoms [11]. Four histamine receptors have been

discovered, with the H₁ [12], H₂ [13] and H₄ [14] receptors found to be involved in ocular allergy. H₁ and H₂ receptor signaling results in pruritus, conjunctival hyperemia, cytokine secretion, fibroblast proliferation, adhesion molecule

expression, microvascular permeability and production of procollagens [4,14-19]. H4 receptor signaling has been shown to affect cytokine and chemokine release, chemotaxis, and adhesion molecule expression [14-18]. While most of the drugs in this class target the H1 receptor, some of the agents also target the H2 and H4 receptors. Topical antihistamines competitively and reversibly block histamine receptors in the conjunctiva [11,19]. The symptomatic relief of antazoline and pheniramine, the first antihistamines to be formulated ophthalmically, tends to be immediate but temporary, and therefore, these agents may require frequent dosing throughout the day. Because first-generation antihistamines are for the most part ineffective against redness, they are not used in isolation but are combined with vasoconstrictors such as naphazoline. The first of these combinations, Vasocon-A, was approved post-marketing by the FDA in 1990 for the treatment of allergic conjunctivitis [20]. First-generation topical antihistamines are lipophilic and could cross the blood-brain barrier, causing central side effects such as sedation [21].

The extensive patient experience with topical combination antihistamine-decongestant products has amply demonstrated their safety and led to their becoming available OTC. These products remain the drugs of choice for self-prescription, and examples are Vasocon-A, Naphcon-A, Visine-A, Opreon-A and Eye Allergy Relief. Although there is a mismatch between the duration of the decongestant and the antihistamine in these formulations, with the former lasting only 1 – 2 h, and the latter, 3 – 4 h [19,20], the immediate relief that patients perceive when using these products has added greatly to their acceptance. It is possible that the drops are taken in periods of acute allergic distress, after which the redness never returns to pre-dose levels, also possibly due to a modest effect of the antihistamine on redness.

Newer-generation topical antihistamines are more potent inhibitors of histamine-stimulated cytokine synthesis in intact conjunctival epithelial cells [19]. The second-generation antihistamine levocabastine was the first to be used in isolation and had a longer duration of action than the first-generation agents, but it has been discontinued in the United States. Levocabastine was also the first antihistamine shown to have multiple mechanisms of action to help reduce the early phase immune response and the late-phase response by reducing eosinophil activation and infiltration [19,22]. Emedastine is another second-generation antihistamine that has a similar duration of action to levocabastine, but it has been shown to be superior for prevention and treatment of allergic conjunctivitis in one prospective clinical trial [23]. The second-generation topical antihistamines have a duration of action up to 4 h and are indicated for four times daily dosing. Emedastine is approved for use in patients 3 years of age or older, and a study also showed emedastine inhibited histamine-evoked increased vascular permeability [19]. While these multi-mechanism, newer-generation antihistamines are no longer available in the US, they started the evolution of the dual-acting agents.

A topical formulation of the second-generation antihistamine, cetirizine, marketed orally as Zyrtec, is being developed for twice-daily use in the prevention of ocular allergic itching and this drug is in its latest stages of preparation for an FDA filing (<http://www.nicox.com/rd/ophthalmic-pipeline/ac-170/>).

3.3 Mast cell stabilizers

While the first-generation antihistamines provided short-term relief of symptoms by blocking the activity of mast cell-released histamine on histamine receptors, first-generation mast cell stabilizers prevent mast cells from degranulating, and thus release of histamine and other mediators is pre-empted. In addition to reducing the direct effects of histamine, mast cell stabilizers have been shown to reduce the influx of monocytes, eosinophils and neutrophils. However, these anti-allergic effects have been difficult to demonstrate in the eye clinically. The main problem with first-generation mast cell stabilizers is that they were developed for ophthalmic use before the concept of mast cell heterogeneity was firmly established. The widely studied effects of these compounds on mast cells were tested preclinically using other species and tissues, and their anti-allergic activity was later found not to be significantly present in human conjunctival mast cells. This lack of efficacy was initially attributed to the necessity of a pre-season loading period [24,25], but the continued use of mast cell stabilizers in the 1980s and 1990s was more a function of a lack of an alternative efficacious therapy than any real benefit.

Several membrane stabilizer drugs exist, such as cromolyn (sodium cromoglycate), nedocromil sodium, pemirolast and lodoxamide, all of which have relatively few local or systemic side effects [24,25]. Cromolyn is the oldest agent in this class, yet its mechanism of action is still unclear. Nedocromil sodium inhibits chloride ion influx in mast cells, epithelial cells and neurons. Pemirolast has been shown to inhibit eosinophil chemotaxis in addition to mast cell degranulation [25,26]. Nevertheless, in human conjunctival mast cells, cromolyn sodium failed to inhibit histamine release and nedocromil was only marginally effective at very high concentrations [26]. While preclinically, lodoxamide was much more potent than cromolyn and also blocked eosinophil chemotaxis [26], this mast cell stabilizer appears to be most efficacious for the epitheliopathy and shield ulcers associated with VKC [27]. The only agent in this class that has shown considerable clinical efficacy in SAC was pemirolast [28].

3.4 Corticosteroids

Glucocorticoids are an effective therapy for various forms of allergic disease, ranging from allergic rhinitis to asthma, and including ocular allergy. Specifically, topical corticosteroids have been reported to be highly effective at treating severe or chronic ocular allergy [29,30]. This efficacy is the result of a variety of effects on the allergic cascade, working on both molecular and cellular targets. The main mechanism of action is inhibition of prostaglandin and leukotriene synthesis by arachidonic acid through blockage of phospholipase A [11].

Corticosteroids have been shown to affect mast cells by inhibiting their proliferation and recruitment [11,31-33]. Steroids also decrease the production of eosinophils, while also inducing their apoptosis and phagocytic destruction [11,31-33]. Numerous other effects include reducing the availability of histamine, both by increasing cellular stores and decreasing the expression of histamine receptors [33]. These robust anti-inflammatory effects come at a cost as ocular side effects can occur with their use. Possible immunosuppression, superinfection, cataract formation, corneal hazing, delayed wound healing, ptosis (steroid myopathy) and increased intraocular pressure (IOP) are some of the adverse effects that need to be considered when administering these medications [34]. There was also a recent publication in a series of children treated with topical fluorometholone in which temporary growth suppression was observed [35].

When SAC is refractive to other treatment options, topical corticosteroids can be recommended for short-term treatment with careful monitoring [11,29]. Medications such as clobetasonebutyrate, dexamethasone, fluorometholone, hydrocortisone, prednisolone, rimexolone and triamcinolone have been used, but concerns regarding increased IOP and cataract formation limit their use [11,30]. Loteprednol etabonate 0.2% (LE), a 'soft steroid,' was developed to limit risks associated with increased IOP and cataract formation [30]. LE is an ester corticosteroid with a 17 β -chloromethyl ester at the carbon-20 position instead of a ketone, a substitution that allows the drug to undergo predictable hydrolysis [36,37]. Two randomized, double-masked placebo-controlled studies found similar safety profiles between LE and placebo [36,37]. Additionally, a retrospective review of 159 patients examined safety in patients using LE daily for > 12 months and found no long-term use associated adverse effects [38].

Ocular Therapeutix has developed technology for encapsulating ophthalmic pharmaceuticals within a hydrogel to deliver sustained therapeutic levels of various drugs via punctal plugs [39]. One of these, OTX-DP, is a dexamethasone depo that has been tested and shows promise for treatment of chronic allergic conjunctivitis modeled by multiple conjunctival allergen challenges (CACs; <https://clinicaltrials.gov/ct2/show/NCT02062905?term=ocular+therapeutix&rank=8>).

Though topical corticosteroids are the most frequently used route for severe ocular allergy, other routes of administration have been explored. Several case reports have indicated improvement with the use of supratarsal injection of corticosteroids in severe VKC [40-42]. A recent retrospective, noncomparative study of childhood refractory allergic keratoconjunctivitis with 35 patients suggested that supratarsal injection of triamcinolone acetonide was effective and safe, with only one patient experiencing elevated IOP [43]. Prospective studies are still needed.

Intranasal corticosteroids (INSs), widely used in the treatment of allergic rhinitis, have also been examined with respect to treating ocular symptoms [44]. The exact mechanism of reducing ocular symptoms is unknown. Three possible

mechanisms have been proposed: the INSs directly enter the eye via the nasolacrimal duct, decreased inflammation of the nasolacrimal duct allows for improved drainage of allergens, or decreased nasal inflammation normalizes the excess reflex neural activity that occurs during allergic reactions [45]. Studies have found lower levels of substance P in tear fluid after use of INSs, suggesting that substance P may have a significant role in naso-ocular interactions in allergic rhinoconjunctivitis [46]. Favorable effects on ocular symptoms were demonstrated in studies of different treatment agents, including mometasone furoate, fluticasone furoate, fluticasone propionate and budesonide [47-51]. This includes a meta-analysis of 10 randomized, placebo-controlled trials showing that mometasone furoate nasal spray was effective at relieving ocular allergy symptoms in patients with allergic rhinitis [51]. Concerns for ocular side effects of INSs are likely due to the safety profile of oral and inhaled corticosteroids, but published data for INSs in patients with rhinitis do not demonstrate an increased incidence of ocular hypertension, glaucoma or cataracts [50].

One study assessed the effects of topical olopatadine and mometasone nasal spray in allergic subjects using the CAC and nasal allergen challenge (NAC) models of allergy. In contrast to the findings described above, CAC was shown to cause clinically significant ocular and nasal signs and symptoms; however, the NAC resulted only in nasal signs and symptoms. With regard to treatment, not surprisingly, ocular olopatadine provided the most effective management of ocular allergy and the nasal spray the most effective management of nasal allergy. In subjects with both nasal and ocular allergy, the combined treatment was the most effective [52].

3.5 Topical NSAIDs

Topical NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2) resulting in inhibition of inflammatory mediators such as prostaglandins and leukotrienes [53]. They alleviate pain, irritation and hyperemia, and are approved for the most part for post-operative inflammation. Several agents have been tested for treatment of ocular allergy, including ketorolac, flurbiprofen, indomethacin and diclofenac; however, they were generally either ineffective or at best inferior to topical antihistamine therapy [2-5,54,55]. Topical NSAIDs are also associated with burning and stinging, so patient compliance can be an issue. Although for inflammation they are to be preferred when possible over corticosteroids, topical NSAIDs are associated with the potentially devastating adverse effect of corneal melting, usually in the context of prior ocular surface disease [56-58].

3.6 Systemic antihistamines

Systemic antihistamine medications have limited applications for ocular allergy. Randomized trials have demonstrated that ocular symptoms are alleviated with greater speed and efficacy by topical antihistamines [52,59,60]. Systemic antihistamines can cause further discomfort by exacerbating ocular dryness

by decreasing tear production and drying mucosal membranes [61]. Though less common with newer generations, there remains the risk of systemic side effects such as sedation and cardiotoxicity [11]. When there are associated nonocular allergy symptoms, such as rhinitis or generalized pruritus, systemic antihistamines can be utilized as an adjunct therapy [11]. There are newer antihistamines such as bilastine that have been shown to have no sedating effects and have been studied in the context of allergic rhinoconjunctivitis with some success [62].

3.7 Immunomodulatory therapy

Immunomodulatory agents alter normal immune pathways and offer a steroid-sparing alternative for allergic conjunctivitis. Several agents have also shown efficacy in various ocular diseases, including cyclosporine A, tacrolimus, mycophenolate mofetil, leflunomide, rapamycin (sirolimus), copaxone, laquinimod and infliximab [63]. Many of these immunomodulatory drugs have shown limited success due to their low water solubility and lipophilic nature resulting in poor corneal penetration [21]. Both cyclosporine and tacrolimus have shown promise in treating severe more chronically inflammatory forms of ocular allergy.

Cyclosporine A inhibits T-cell activation as well as eosinophilic infiltration into the conjunctiva and interferes with both late-phase and delayed-type allergic reactions [64,65]. A small prospective double-masked randomized comparative trial between cyclosporine 2% eye drops and tacrolimus 0.1% ointment found that both were effective in treating VKC [66]. A large prospective, observational study of patients with severe VKC and AKC found that cyclosporine 0.1% was safe and effective [67]. A small randomized, placebo-controlled trial showed that topical cyclosporine 2% was an effective steroid-sparing agent, but intense stinging associated with drop instillation limited patient tolerance [68].

Tacrolimus inhibits T-cell activation with a potent immunosuppressive effect, which has been shown to be up to 100 times stronger than that of cyclosporine *in vitro* [69]. A randomized, placebo-controlled clinical trial with tacrolimus 0.1% suspension in 56 patients with VKC/AKC refractory to conventional treatment showed that tacrolimus caused marked improvement in objective signs and was well tolerated by patients [70]. The most frequent treatment-associated adverse effect was mild ocular irritation, noted in 42.9% of patients in the treatment group [70]. Ointment formulations of tacrolimus have also been shown to be efficacious as a steroid-sparing agent in both 0.1 and 0.03% concentrations [65,71].

3.8 Dual acting agents

Dual-acting H1 receptor antagonist and mast cell stabilizer agents include olopatadine, ketotifen, azelastine, epinastine, bepotastine and alcaftadine. These agents also help prevent eosinophil infiltration. Olopatadine and ketotifen are commonly used for multiple types of ocular allergy. Olopatadine

0.1% (Patanol[®]) was the first topical anti-allergic medication, which was approved by the FDA for twice-daily dosing [21]. Ketotifen is used in several OTC anti-allergy drops. Azelastine has an additional mechanism of action involving inhibition of platelet-activating factor and expression of intercellular adhesion molecule 1, both of which contribute to its efficacy in PAC [72]. Epinastine competitively blocks both H1 and H2 receptors, activity which may help reduce eyelid edema [73]. Epinastine also does not cross the blood-brain barrier, should not cause any CNS side effects, and, as opposed to ketotifen, has been shown to cause no effect on working memory in children [74]. Another distinction between topical antihistamines is drop comfort: for example, patients report olopatadine and epinastine are more comfortable than azelastine, and epinastine is more comfortable than ketotifen [19]. Another study of 66 patients treated with bepotastine versus placebo illustrated a statistically significant decrease in nonocular-associated symptoms, including nasal congestion, rhinorrhea, ear/palate pruritus and nasal pruritus [75]. All drugs in this class reduce ocular pruritus for up to 8 h, allowing twice-daily dosing, and olopatadine 0.2% is approved for once-daily dosing.

Alcaftadine has a unique pharmacological profile with activity against H1, H2 and H4 receptors [76], as well as reducing conjunctival eosinophil infiltration and the late-phase immune response [77]. Olopatadine 0.2% and alcaftadine are the only anti-allergic agents available for once-daily dosing. Very recently (February 2015), the FDA approved a higher dose of olopatadine (0.77%, Pazeo[™]) developed by Alcon in conjunction with Torkildsen and Ora, also for once-daily dosing.

Two papers have been published recently investigating the efficacy of alcaftadine 0.25% compared with 0.2% olopatadine (Pataday[®]) [78,79]. The earlier paper presented the results of one multicenter, double-masked, active- and placebo-controlled CAC trial in 127 subjects. Onset and duration of action at 16 and 24 h after dosing were established. For the primary measure of ocular itching, both actives were statistically significantly superior to placebo at all time points post-CAC for both the 16- and 24- h duration assessments ($p < 0.0001$). This confirms that both olopatadine 0.2% and alcaftadine 0.25% are effective for symptomatic prevention of itching, all day, for up to 24 h. However, at the peak time post-CAC for itching, 3 min after challenge, alcaftadine treatment resulted in significantly lower mean itching scores at the 16-h duration assessment ($p = 0.026$). Furthermore, only alcaftadine provided significant relief of chemosis at every time point 24 h after dosing [78].

The second alcaftadine versus olopatadine paper published in 2014 was on a pooled analysis of two CAC studies performed in 284 subjects. Again, at 16 h after instillation, alcaftadine was superior to olopatadine 0.2% for the first explosive itching that occurs at 3-min after allergen challenge (0.50 vs 0.87, respectively, $p = 0.0006$). Alcaftadine also demonstrated lower mean itching scores over all time points

(0.68 vs 0.92 respectively, $p = 0.0390$) compared with Pata-day. Finally, minimal itching (a score < 1) was reported in 76.1% of alcaftadine-treated subjects versus 58.1% of olopatadine-treated subjects ($p = 0.0121$) [79].

4. Current research for future therapy

4.1 Allergen desensitization

Subcutaneous allergen desensitization is currently used for the treatment of allergic rhinitis and asthma. It has been shown to improve conjunctivitis symptoms in rhinoconjunctivitis [80]. Sublingual immunotherapy (SLIT), an off-label form of allergen desensitization using grass allergen tablets, has been widely studied for allergic rhinitis and has also been shown to be safe and effective [81,82]. A recent Cochrane review focused on allergic conjunctivitis and on ocular symptoms in allergic rhinoconjunctivitis in randomized trials involving SLIT [82]. It concluded that SLIT was effective in reducing ocular symptoms, although it did not show a reduction in the use of topical ophthalmic medications [83]. A Phase III study involving an experimental SLIT, MK-8237 from Merck, is currently underway with a focus on allergic rhinitis with or without allergic conjunctivitis [84]. Further research is needed to determine optimum dosing and elucidate SLIT's role in the treatment of allergic conjunctivitis.

4.2 Selective glucocorticoid receptor agonists

Selective glucocorticoid receptor agonists (SEGRAs) are a relatively recent therapeutic option in development [85-90]. As previously mentioned, prolonged use of topical corticosteroids can be associated with severe side effects, the existence of which prompted investigation of alternative agents that selectively target glucocorticoid receptors (GRs). Corticosteroids bind to the GR and appear to regulate gene expression through at least two intracellular mechanisms, transrepression and transactivation [86,87]. Additional research is needed to further elucidate the relevance of these mechanisms, as both appear to participate in the anti-inflammatory effect of corticosteroids [88], and transactivation has been associated more with adverse effects [90]. This mechanism appears to initiate an accumulation of extracellular material in outflow channels of the trabecular meshwork, which could be responsible for corticosteroid-induced IOP elevation [91,92]. SEGRAs have been designed to target these mechanisms and potentially reduce harmful side effects. *In vitro* and animal studies involving SEGRAs, such as mapracorat and ZK209614, have the potential to be used for the treatment of ocular allergy [32,93].

4.3 Toll-like receptors

Toll-like receptors (TLRs) have been shown to be present in cells of the cornea and conjunctiva and are being investigated as a target for new medications [94,95]. Many immune system cells express TLR, including mast cells and eosinophils, and it is theorized they cause the release of mediators that interact with lymphocyte equilibrium leading to allergic disease states.

Compounds that downregulate the TLR signaling pathway, such as TLR antagonists or TLR-co-receptor antagonists, are being studied for their anti-allergic activity. These compounds include pyrimidine derivatives, oligodeoxynucleosides, anti-histamines, leukotriene antagonists, mast cell stabilizers, anti-IgE agents, a vitamin D receptor ligand, a quinazoline derivative and a TLR antibody [21,94,95]. TLR3 on ocular surface epithelial cells in particular, appears to be critical to the development of an eosinophil-driven late-phase reaction [95].

4.4 Other potential targets

There are numerous other anti-inflammatory targets being evaluated for ophthalmic diseases. Spleen tyrosine kinase or Syk, has been shown to have a role in mast cell degranulation, eosinophil recruitment and cytokine production with implications that it has a role in allergy [96]. Similarly, JAK has been evaluated for its role in allergic reactions [97]. Acix Therapeutics and Portola Pharmaceuticals are developing three kinase inhibitors for allergic conjunctivitis, which have had success in preclinical models: PRT02070, a combination JAK/Syk inhibitor, and PRT02761 and PRT02607—two Syk-specific inhibitors [98]. The cytokine IL-1 plays a central role in the initiation of the immune system and its blockade could represent another target in treatment of allergic conjunctivitis [98-100]. IL-1 signaling inhibitors, such as topical anakinra and EBI-005, are currently being developed for the treatment of dry eye disease [99]. An animal study implicated that IL-1 receptor antagonists suppress allergic eye disease by down-regulating the recruitment of eosinophils and other inflammatory cells [100]. Eleven Biotherapeutics has completed a clinical study on an IL-1 receptor antagonist in a model of moderate-to-severe allergic conjunctivitis using both an environmental exposure chamber and modified conjunctival allergen provocation test (CAPT) (clinicaltrials.gov: NCT02082899). A recent press release (<http://ir.elevenbio.com/releasedetail.cfm?releaseid=874221>) reported that the primary end point of ocular itching was not demonstrated in the CAPT model, so it remains to be seen what the clinical relevance of these IL-1 antagonists will be for the treatment of chronic allergy or PAC.

5. Conclusion

Allergic conjunctivitis is a common disease with numerous factors affecting its symptomatology. Our understanding of the complex immune system response to allergens dictates the development of medications for the disease. Several classes of drugs are currently available which target different immune mediators and receptors to alleviate the burden of the disease. Topical, systemic and other nonocular treatments have been developed and are often used in combination to help control the disease process. Topical antihistamines and dual-acting agents are among the most common drugs used for ocular allergy. For more severe disease, corticosteroids and immunomodulatory molecules may be necessary to alleviate signs and

symptoms and prevent further sequelae. Allergen desensitization may also play a role in ocular allergy as it does in other types of allergy such as allergic rhinitis and allergy-induced asthma. Several newer targets are also being studied, and many novel drugs are currently under investigation that will add to the allergic conjunctivitis treatment armamentarium.

6. Expert opinion

The symptoms and signs of allergic conjunctivitis vary widely as a function of genetics, environmental exposure and the patient's individual immune response. In some patients, symptoms predominate without a clear presentation of signs; however, the presence of ocular itching is pathognomonic. Allergens also vary greatly throughout the year and in different regions of the world, and the co-presence of pollution can lead to a more complex and chronic presentation. The variability inherent in ocular allergy presents some difficulty in the evaluation of efficacy of drug therapy. Clinical studies of potential anti-allergic drugs evaluate subjects either in seasonal studies with natural, environmental allergen exposure or via CAC. Seasonal studies are wrought with uncontrollable factors such as allergen exposure; time spent outdoors, inadequate or inaccurate completion of diaries for real-time, at-home assessments of symptoms, and the impossibility of guaranteeing the presence of signs and symptoms at the time of the in-office assessments. Furthermore, a recent report evaluated seasonal studies from 1965 to 2010 and found that objective patient inclusion criteria and outcome measures were very limited [101]. Only a minority of the trials was randomized, masked, and placebo-controlled, and only a small percentage was multicenter. Several outcome measures such as recurrence rate or disease relapse were not studied in the majority of the studies. In contrast, the CAC allows for a standardized method of allergen exposure and an accurate, in-office real-time assessment of signs and symptoms at drug onset and in defined time periods after drug instillation to assess duration of action. All environmental variables and allergen exposure are held constant, and a drug effect is revealed with much greater accuracy and reproducibility.

There are many therapies currently available for the various types of ocular allergy. While short-acting, some of the

first-generation medications developed decades ago are still effective and currently in use in OTC preparations. Newer-generation antihistamines and dual acting agents are the mainstays of current management of allergic conjunctivitis. Only two drugs are presently available for once-daily dosing: olopatadine 0.2% (Pataday®) and alcaftadine 0.25% (Lastacaft®). Given the nature of SAC and PAC, the constant control of symptoms offered by these drugs sets the bar high for all other molecules. In head-to-head comparisons, it appears that alcaftadine has a greater control of itching at its peak, and a greater percentage of subjects are maintained at minimal levels of symptoms [78,79].

There is abundant research into the immunopathogenesis of allergy. As our understanding of the involved immune mediators and pathways expands, so does the potential scope of therapeutic modalities. Novel drug targets are being discovered and new molecules are in various stages of development. SEGRAs and drugs targeting TLRs, IL-1, Syk and JAK are showing some evidence of efficacy. Some new compounds affect more than one pathway and thus have multiple mechanisms of action and beneficial effects. Continual comparison of the clinical efficacy of available molecules in masked, randomized controlled trials will guarantee that the best drug is being offered to patients. In addition to studying efficacy, better evaluation of the safety, side effect profile and tolerance of drugs may also help determine which should be used in practice. With improved knowledge of immunopathogenesis, larger clinical trials of current medications and continued development of novel drugs, the ideal treatment algorithm for ocular allergy is on the horizon.

Declaration of interest

MB Abelson is the Founder and Chief Scientific Officer of Ora, Inc. Ora, Inc. has received or is receiving financial consideration in connection with certain ocular allergy therapeutics. L Smith is an employee of Ora, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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