# Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management

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**Stacey Ackerman, Lisa M. Smith and Paulo J. Gomes**

***Abstract*:** Allergic conjunctivitis is one of the most common allergic conditions worldwide. Its incidence is increasing due to changing climate, pollution, increased pollen loads, and the subject's heightened immunological sensitivity in response to these environmental changes. The pathophysiology predominantly involves immunoglobulin E-related mast-cell activation, with release of histamine and other mediators contributing to the propagation of the response by calling in other immune cells and further inflammation. This article presents the evolution of ocular allergy treatments, from vasoconstrictors, to antihistamines and mast-cell stabilizers, to the dual-acting agents, as well as corticosteroid and immunomodulatory options. Future targets for allergy treatment are also discussed.

***Keywords:*** ocular itching, histamine, mast cell, IgE, allergic conjunctivitis, CAC, antihistamines, alcaftadine, olopatadine

## Introduction

Allergic conjunctivitis (AC) has an increasing prevalence worldwide. Ocular itching is the pathognomonic symptom of AC, enabling its differential diagnosis from other ocular conditions arising from nonallergic irritations [Spangler *et al.* 2003; Leonardi, 2013; Miraldi Utz and Kaufman, 2014]. As subjects may accept their AC symptomology as 'normal' until alleviated by an ocular anti-allergic regimen, there is little doubt that the incidence of ocular allergy is underreported and undertreated [Williams *et al.* 2013].

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common forms of ocular allergy subsets and they are estimated to affect 15–25% of the US population [Ono and Abelson, 2005; O'Brien, 2013; Miraldi Utz and Kaufman, 2014]. In Europe, AC is on the rise, affecting as much as 50% of the population, possibly due to the introduction of ragweed in 2009 [Burbach *et al.* 2009].

The contributory role of air pollution has received attention of late, including analysis of the effects of exposure to hydrocarbons and automotive exhaust on the conjunctival immunological response [Wang *et al.* 2011; Brandt *et al.* 2013; Fujishima *et al.* 2014; Guarnieri and Balmes, 2014]. The urbanization of Europe certainly might be a contributing factor to the increasing prevalence of AC in this region.

Comorbidity of AC and rhinitis is well recognized. The percentage of undiagnosed AC in patients presenting with rhinitis may range from 25% to 60% [Bauchau and Durham, 2004]. When considering patients with rhinitis, asthma, and other atopic conditions [Petricek *et al.* 2006; Williams *et al.* 2013; Gomes, 2014; Miraldi Utz and Kaufman, 2014], this incidence increases to 40–80%.

## The pathognomonic symptom with clinical consequences

AC patients typically present bilaterally with itching, lacrimation, burning, vasodilation, and chemosis [Ciprandi *et al.* 1992; Abelson *et al.* 2003], however, it can be asymmetrical. Patients consider ocular itching the most disruptive symptom of AC [Gomes, 2014], and may also complain of

Correspondence to:
**Stacey Ackerman, MD**
Philadelphia Eye Associates, 1113 Hospital Drive, Suite 302, Willingboro, NJ 08046, USA
**staceyackermanmd@aol.com**

**Lisa M. Smith, BS**
**Paulo J. Gomes, MS**
Ora, Inc. Andover, MA, USA

a concomitant foreign body sensation, blurring, and photophobia if there is corneal involvement. Rubbing the eyes augments the intensity and duration of itching, chemosis, and hyperemia [Raizman *et al.* 2000]. A conjunctival papillary reaction is most typical, however, a follicular reaction may be more diagnostic of a medication-related allergy, for example, to brimonidine or neomycin.

AC is differentiated into a spectrum from the benign SAC, PAC, and giant papillary conjunctivitis (GPC) to the chronic, morbid, and potentially sight-threatening vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and contact blepharoconjunctivitis (CBC). The acute or subacute symptoms of SAC fluctuate with temporal exposure to the offending airborne environmental antigens, which are typically tree pollens in early spring, grasses in May through July, and weed pollens and outdoor molds from August through October [Leonardi, 2013; Fujishima *et al.* 2014; Miraldi Utz and Kaufman, 2014]. The persistent symptoms of PAC arise from singular and/or multiple indoor allergens, such as animal dander, molds, and dust mites. Reactions are exacerbated by prolonged or concentrated allergenic exposure, and often, comorbidity with dry-eye syndrome [Leonardi, 2013; Miraldi Utz and Kaufman, 2014].

GPC is a hypersensitivity reaction typically caused by contact lens wear, but can be associated with ocular prostheses, postoperative sutures, or some ocular surface irregularities. Clinical symptoms may include mild to intense itching, a foreign body sensation, mucous discharge, blurring, excessive contact lens movement, and photophobia [Leonardi, 2013; Miraldi Utz and Kaufman, 2014]. GPC is also characterized by giant papillae ($>$ 1 mm), predominantly on the tarsal conjunctival surface that abuts the offending foreign body [Leonardi, 2013; Miraldi Utz and Kaufman, 2014], therefore usually favoring the upper palpebral conjunctival surface. Even after removal of the offending agent, patients may be left with permanent evidence of GPC.

Chronic and severe, VKC typically manifests in children and adolescents in the hot, dry climates of equatorial regions, predominating in boys with a 3:1 ratio. Approximately 50% of VKC patients have histories of atopy, for example, asthma, allergic rhinitis, or eczema [De Smedt *et al.* 2013; Emre *et al.* 2013; Leonardi, 2013; Gomes, 2014; Miraldi Utz and Kaufman, 2014]. The diagnostic features are tarsal papillae and limbal gelatinous infiltrates with exacerbation by allergenic re-exposure and/or sunlight, wind, and dust [Leonardi, 2013; Gomes, 2014; Miraldi Utz and Kaufman, 2014].

Chronic inflammation of the eyelid, conjunctiva, and possibly the cornea, characterizes AKC, which appears primarily in adults 30–50 years of age, concurrent with multiple systemic atopic diseases, such as allergic dermatitis, eczema, and allergic asthma [Leonardi, 2013; Chen *et al.* 2014]. Patients may have an ectropion of the lower lid. Other complications include conjunctival fibrosis, *Staphylococcus aureus* colonization of the eyelid, herpetic keratitis, keratoconus, retinal detachment, and cataracts with possible associated vision loss [Leonardi, 2013; Miraldi Utz and Kaufman, 2014].

## The pathophysiology of AC

SAC results from a classic type I hypersensitivity reaction [Miraldi Utz and Kaufman, 2014]. Allergen permeates the protective conjunctival epithelial layer and crosslinks two adjacent immunoglobulin E (IgE) molecules on the surface of mast cells. This crosslinking prompts mast cells to degranulate and release inflammatory mediators, particularly histamine, responsible for ocular itching, hyperemia, inflammation, tearing, and chemosis [Collum and Kilmartin, 2000; Abelson *et al.* 2003; Akdis and Blaser, 2003]. This continued histamine and allergen load leads to an increased population of resident mast cells in conjunctival tissue both during and after the pollen season [Anderson *et al.* 1997].

PAC differs from SAC in that the persistent IgE-mediated degranulation of mast cells prompts the recruitment of eosinophils [Miraldi Utz and Kaufman, 2014]. PAC also tends towards chronicity due to the continued exposure to allergen throughout the year, and chronic inflammation can ensue. VKC and AKC embody both type I and type IV hypersensitivity reactions, the latter a delayed, cell-mediated reaction. VKC is particularly characterized by T cell-mediated responses and increased concentrations of conjunctival T cells [Solomon *et al.* 2001]. Eosinophil recruitment is also evident in VKC and AKC [Leonardi, 2013].

GPC is characterized by a T cell-mediated response consequent to mechanical trauma to the

conjunctival epithelium, although allergenic substances deposited on the contact lens and/or foreign body may induce an associated type I hypersensitivity [Miraldi Utz and Kaufman, 2014]. CBC is also a type IV, T cell-mediated hypersensitivity response to an antigenic complex formed between the offending substance complexing other proteins. The sensitization process develops over weeks or months and the 'acute' response requires 48–72 h to manifest; however, responses to mechanical irritation from foreign bodies or lenses may require only 2–3 h [Leonardi, 2013; Miraldi Utz and Kaufman, 2014].

### *The cellular components of the allergic response*

Mast cells are the principal cellular components and primary instigators of the allergic response. Crosslinking of IgE molecules on mast-cell membranes initiates degranulation and the consequent release of histamine and other mediators [Solomon *et al.* 2001; Leonardi, 2002; Namdar and Valdez, 2011]. Mast-cell activation is key to the pathophysiology of SAC, PAC, VKC, AKC, and GPC [Leonardi, 2002; Saban *et al.* 2013]. While the immediate onset of ocular itching is directly the result of mast cell-released histamine, the release of companion proinflammatory mediators attracts neutrophils, T cells, basophils, and eosinophils, which all amplify later stages of the allergic response [Leonardi, 2002; Miraldi Utz and Kaufman, 2014].

Whereas mast cells permanently reside in conjunctival tissues, basophils circulate in the blood and migrate to sites of inflammation when called in by locally released chemokines. Basophils also express the IgE receptor; they secrete histamine along with other mediators, and play a key role in the development and maintenance of allergic inflammation. Eosinophils also migrate to sites of chronic inflammation, contributing to structural damage and fibrosis by secreting cytotoxic proteins and cytokines. Increased concentrations of T cells may be present in SAC and PAC, although mast cells seem capable of instigating IgE production independently of T cells [Bonini *et al.* 1993; Leonardi, 2002]. T cells are the prime players in all the more severe allergic diseases.

### *Mediators of the allergic response*

While histamine remains the principal causative agent of the clinical manifestations of type I reactions, other mediators include tryptase, leukotrienes, prostaglandins, cytokines, chemokines, proteases, growth factors, and adhesion molecules. These all initiate innumerable intracellular signals that further activate inflammatory and structural cells, as well as receptors on vasculature and nerves that ultimately lead to the signs and symptoms of allergic inflammation [Leonardi, 2013; Saban *et al.* 2013].

Surprisingly, it was not until 1981 that the primary role of histamine in ocular itching was proven [Abelson and Udell, 1981; Abelson and Schaefer, 1993]. Itching is thought to be primarily mediated by activation of H1-histamine receptors [Leonardi, 2000; Solomon *et al.* 2001], however, other mediators and receptors probably contribute to ocular itching since it is not completely alleviated by H1-receptor antagonists [Andoh *et al.* 2012]. Leukotriene B4 (LTB4) was identified as a mediator of ocular itching in a mouse model, suggesting that therapeutic agents that inhibit the production or release of LTB4 might have enhanced antipruritic activity [Samuelsson *et al.* 1987; Andoh *et al.* 2012; Saban *et al.* 2013].

While innumerable cytokines have a definitive role in the allergic response, their specific and differential activity has not yet been clearly elucidated. Many cytokines, such as interleukin (IL)-4, IL-5, IL-6, IL-8, IL-13, as well as chemokines, and their receptors are overexpressed in SAC and PAC, but identifying direct therapeutic targets has proven elusive [Solomon *et al.* 2001; Leonardi, 2002; Namdar and Valdez, 2011]. In tears, the proteinase tryptase is considered a biomarker for IgE-mediated allergic conjunctival responses [Leonardi, 2013]. Tryptase is thought to activate other proteases involved in extracellular matrix degradation and inflammatory cell infiltration [Butrus and Wun, 2000]. The intercellular adhesion molecule-1 (ICAM-1) is stimulated by inflammatory cytokines, and propagates the allergic cascade by facilitating the transmigration of inflammatory cells into conjunctival tissue [Abelson and Kaplan, 2002]. In a murine model of allergic conjunctivitis, eosinophil infiltration has also been demonstrated to be mediated by very late antigen-4 and its ligand, vascular cell adhesion molecule (VCAM)-1 [Fukushima *et al.* 2006]. Some anti-allergic agents block the interaction between $B_1$ integrins and VCAM-1, and this is a potentially promising future target for small molecule antagonists [Baiula *et al.* 2012].

### *The acute and chronic allergic responses*

The ocular allergic response has two temporal components, the early phase and the late-phase reaction. The early phase reaction is driven by histamine and associated inflammatory mediators released from activated mast cells [Williams *et al.* 2011; Leonardi, 2013]. This acute reaction gives rise to immediate clinical symptoms. In tears, histamine concentrations peak 5 min postexposure after a single episode of allergen exposure, and the clinical reaction subsides naturally over the course of 30–40 min [Leonardi, 2002; Fujishima *et al.* 2014].

The late-phase allergic reaction develops approximately 6–72 h after allergen exposure in consequence to the accumulation of inflammatory cells (e.g. basophils, eosinophils, T cells, and neutrophils) within the conjunctiva [Solomon *et al.* 2001; Leonardi, 2013; Saban *et al.* 2013]. The release of inflammatory mediators, such as IL-4, which upregulates IgE production and T-cell growth and differentiation, also drives the late-phase reaction [Solomon *et al.* 2001]. The histamine peak accompanying the late-phase reaction is often attributed to mast cells, but basophils might predominate because tryptase values (i.e. released by mast cells) do not peak during the late-phase reaction [Leonardi, 2002; Saban *et al.* 2013]. Nevertheless, in the natural environment, these early and late-phase processes are juxtaposed continually with continued exposure [Solomon *et al.* 2001; Fujishima *et al.* 2014].

### *The origin of itch*

The sensation of itch is differentiated by the distinct coding properties of itch and pain neurons and their differential innervation. A recent review provided a fascinating discussion of the neurobiology of itch, focusing on the advancements of the past few years [Hoon, 2015]. Histamine is both algesic and pruritic, producing itch at the most superficial dermal/nasal/ocular level and pain when injected into deeper levels. Specific nerve cells, called pruriceptors, are responsible for propagating itch stimuli, and these are mediated by histamine H-1 and H-4 receptors [Rossbach *et al.* 2011], as well as receptors for serotonin and protease-activated receptor 2 [Kim *et al.* 2008]; all of these are G protein-coupled receptor (GPCR)-based pathways. These itch-responsive GPCRs trigger G protein-coupled signaling cascades, ultimately activating transient receptor potential-ion channel-mediated pathways. Other non-GPCR-associated pruriceptors have also been identified, including thymic stromal lymphopoietin (TSLP) and its receptors TSLPR and IL7Ra. IL-31 also appears to have a role in itch signaling *via* a subset of Il-31Ra-expressing sensory neurons. Toll-like receptors may also contribute to itch-like sensations [Hoon, 2015].

Activation of sensory neurons is necessary for itch, but recent evidence suggests that the spinal cord mediates itch information to the brain, and without this intermediate there would be no itch sensation. The activation of spinal glutamate-sensitive neurons has been implicated in this itch signaling pathway, as have the natriuretic precursor peptide B (NppB) and its receptor Npr1 [Mishra and Hoon, 2013]. From studies on the origin and circuitry of peripheral itch, it appears that initial stages are characterized by the requirement for NppB and postsynaptic expression of the receptors (Npr1). These Npr1 neurons in turn release glutamate, activating tertiary glutamate receptor-expressing cells. These then directly or indirectly send projections to the higher brain centers. Inhibitory feedback loops are also present to inhibit this itch response [Hoon, 2015].

## Historical and current treatment options

Surprisingly, a recent poll revealed that current trends for the treatment of ocular allergies have little concordance with current recommendations. Specifically, of 2687 polled subjects, 43% used over-the-counter (OTC) topical decongestants, 41% used corticosteroids, 29% used topical antihistamines, 27% used systemic antihistamines, and 15% used mast-cell stabilizers. About 60% of subjects used more than one medication. In fact, 40% of patients used a combination of decongestants and corticosteroids for ocular allergy, independent of the specific diagnosis [Leonardi *et al.* 2015]. Thus, the habitual use of legacy medications persists in the face of evolved options having greater efficacy against ocular itching.

### *Vasoconstrictors – the old guard*

The current predominance of topical vasoconstrictors (decongestants) is astonishing as they were the first agents approved for the treatment of AC. While tetrahydrozoline was marketed as early as the 1950s, in 1971, naphazoline (Vasocon®, Novartis, Basel, Switzerland) was introduced on prescription for the treatment of ocular allergy.

Other formulations of naphazoline and also oxymetazoline were later approved in the 1970s [Williams *et al.* 2011].

Presumably, patients today utilize OTC topical decongestants as a first-line treatment in the absence of medical consultation. Of course, vasoconstrictors alleviate only hyperemia, offering little to no relief of itching [Abelson *et al.* 1980]. Moreover, their efficacy is of short duration, and their use is subject to tachyphylaxis [Abelson *et al.* 1990b; Owen *et al.* 2004; Williams *et al.* 2011; La Rosa *et al.* 2013]. Low-dose brimonidine is a longer-acting alpha-2 agonist formulated in a much lower concentration than that approved for the treatment of glaucoma, and it is in its final stages of development for the treatment of ocular redness (https://clinicaltrials.gov/ct2/show/NCT01959230?term=brimonidine+ocular+redness&rank=1). Alpha-2 agonists such as brimonidine have the advantage over alpha-1 agonists of minimum tachyphylaxis and rebound redness [Vaidyanathan *et al.* 2010].

Ocular decongestants were paired early on with topical antihistamines such as pheniramine and antazoline to combat both the itching and redness associated with AC. Although these combinations reversibly blocked histamine receptors, controlling ocular itching and conjunctival hyperemia, they had no effect on the other proinflammatory mediators, such as the prostaglandins and leukotrienes [La Rosa *et al.* 2013]. The first-generation antihistamines also cause considerable stinging and the short durations of the single agents remained a limitation [Williams *et al.* 2011]. In the mid 1980s, the US Food and Drug Administration (FDA) revoked approval of these grandfathered combination products if pharmaceutical companies did not prove the efficacy and use rationale for each component. These constraints prompted the inception of the conjunctival allergen challenge model for proving efficacy of the antihistamine/decongestant combinations [Abelson *et al.* 1990a]. The conjunctival allergen challenge model continues to be used today as a basis of approval for new anti-allergic treatments.

Systemic antihistamines were also historically popular for the treatment of ocular conditions, prescribed as they were as comprehensive therapy for rhinitis, sinusitis, and other forms of nonsite-specific allergy. The first-generation treatments were known for their sedating and anticholinergic effects; informing patients of potential drowsiness was a warning associated with their use [Allansmith and Ross, 1990].

### *Second-generation antihistamines*

Second-generation antihistamines were introduced in the 1990s. The most efficacious and commercially successful were the topical ophthalmic eye drops, levocabastine and emedastine, and the oral systemic loratadine and fexofenadine.

Levocabastine (Livostin®, Novartis) and emedastine (Emadine®, Alcon, Hünenberg, Switzerland) were indicated for the temporary relief of the signs and symptoms of SAC and AC, respectively. Levocabastine was approved in 1993, emedastine in 1997. These molecules lacked the stinging discomfort of first-generation antihistamines, had improved durations of efficacy (up to 4 h), and had greater specificity for H1-histamine receptors, that is, they had little or no effect on dopaminergic, adrenergic, or serotonergic receptors [Alcon, 1999; Solomon *et al.* 2001]. Levocabastine was a notable advancement in pharmacology because it inhibited the upregulation of eosinophil activation and infiltration. It was, thus, the first topical antihistamine with multiple mechanisms that impacted both the early and late-phases of ocular allergic reactions [Qasem *et al.* 2008; Williams *et al.* 2011], a trait also later shared by the topical competitor emedastine [Abelson and Kaplan, 2002].

The systemic antihistamines, loratadine (Claritin®, Schering-Plough Corporation, Kenilworth, NJ, USA), approved in 1993 for the relief of nasal and nonnasal symptoms of SAC, and fexofenadine (Allergra®, Sanofi-Aventis US, Bridgewater, NJ, USA), approved in 1996 for the relief of symptoms associated with SAC, and whose indication included children 2 years of age or older, were also a notable advancement in pharmacology.

The great boon of the oral antihistamines was that they allowed once-daily dosing, compared with the four times daily dosing required of the contemporary topical agents, and their selectivity for the H1-receptor eliminated most of the sedative effects. The caveats were impairment of fexofenadine bioavailability by fruit juices (e.g. grapefruit, orange, and apple), and their usage still was associated with dry-eye symptoms, which potentially exacerbate ocular AC symptoms [Allansmith and Ross, 1990; Apotex, 2001; Welch *et al.* 2002; Sanofi-Aventis, 2007].

In direct comparison, topical ophthalmic therapy with emedastine proved more efficacious in the reduction of ocular itching (and hyperemia) than oral loratadine; exemplifying the accepted superiority of topical over oral agents for the relief of ocular symptoms [Abelson and Kaplan, 2002]. Nevertheless, approximately 27% of patients currently employ systemic antihistamines [Leonardi *et al.* 2015]; presumably patients utilize OTC systemics as first-line treatment in absence of medical consultation.

### *Mast-cell stabilizers*

Cromolyn sodium (Opticrom®, Allergan, Irvine, CA, USA; also known as sodium cromoglycate), the first drug of this class, was approved in 1984 for the treatment of VKC. Lodoxamide (Alomide®, Alcon), another prominent single-component mast-cell stabilizer with an identical indication, was approved in 1993. In direct comparison, lodoxamide demonstrated greater potency and rapidity of action than cromolyn sodium [Fahy *et al.* 1992]. Lodoxamide also appears to be more efficacious against the epithelial damage and shield ulcers related to VKC [Santos *et al.* 1994].

The next challenger on the market was nedocromil sodium (Alocril®, Allergan), approved in 1999 with the unique indication for ocular itching associated with AC. In turn, nedocromil also demonstrated greater efficacy than cromolyn sodium [El Hennawi, 1994].

The mechanism of action of mast-cell stabilizers is still not clear; they may reduce degranulation and/or biosynthesis of inflammatory mediators *via* a reduction of cellular calcium influx [Cook *et al.* 2002; Leonardi, 2002; La Rosa *et al.* 2013]. Another suggestion is that they inhibit IgE production [Loh *et al.* 1994; Alton and Norris, 1996]. Although efficacious, due to their slow onset of action, the single-component mast-cell stabilizers require a preloading period and are not effective against existing symptoms [Namdar and Valdez, 2011; La Rosa *et al.* 2013]. Given the preloading requirement in the absence of symptoms, poor compliance can be an issue with single-component agents [Butrus and Portela, 2005]. Dual-component agents that combined mast-cell stabilizers with antihistamines provide immediate relief, and these dual-action agents are now the most effective on the market.

### *Nonsteroidal anti-inflammatory agents*

The efficacy of topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of ocular itching secondary to AC lies in their ability to inhibit prostaglandin and leukotriene production. Specific prostaglandins lower the conjunctival threshold for histamine-induced itching, and the prostaglandins may be pruritogenic themselves as well [Blaho, 1992; Woodward *et al.* 1996; Masferrer and Kulkarni, 1997; Donshik *et al.* 2000; Solomon *et al.* 2001; Leonardi, 2013; Saban *et al.* 2013].

NSAIDs commonly prescribed for ocular allergy include ketorolac (Acular®, Allergan), diclofenac (Volteran®, Novartis), indomethacin, and flurbiprofen (Ansaid®, Pharmacia and Upjohn, Kalamazoo, MI, USA). However, only ketorolac is indicated for the temporary relief of ocular itching due to SAC, and has stood as the gold standard for the class [Swamy *et al.* 2007; Kim *et al.* 2010]. Ketorolac is the only NSAID approved for the treatment of seasonal allergic rhinoconjunctivitis [Tinkelman *et al.* 1993]. Nevertheless, topical formulations of indomethacin, ketorolac, and diclofenac have demonstrated efficacy in the treatment of VKC [Kim *et al.* 2010].

### *Corticosteroids*

Topical corticosteroids do not effectively treat the early phase allergic reaction [Gallois-Bernos and Thurmond, 2012], but suppress the late-phase reaction by inhibiting the production and/or release of the inflammatory mediators [Leonardi, 2002; Korenfeld *et al.* 2009]. Topical corticosteroid administration is best reserved for use in patients with refractory symptoms (e.g. VKC and AKC) wherein the inflammation is chronic, allergen-independent, and T cell-mediated, with eosinophil and neutrophil infiltration into the epithelium and stroma. Less potent therapies are ineffective against this more extreme pathology, leaving the risk of corneal involvement extant [Saban *et al.* 2013]. Although, under these clinical circumstances, glucocorticoid administration is justified, long-term use is associated with potentially serious side effects that can be sight-threatening in themselves such as increased intraocular pressure (IOP) and risk of cataract formation. Nevertheless, their clinical usage as eye drops and ointments is widespread, and supervision by an ophthalmologist is necessary [Wilhelmus, 1987; AAO, 2011].

The popular agent loteprednol (Lotemax®, Bausch and Lomb, Bridgewater, NJ, USA), approved in 1998 for the treatment of AC, is representative of the new class of corticosteroids that reduce the risk of increased IOP by being rapidly converted into inactive metabolites following corneal penetration [Druzgala *et al.* 1991]. Loteprednol was evaluated specifically for the treatment of SAC prior to obtaining marketing approval, and demonstrably reduces ocular itching and hyperemia [Dell *et al.* 1998; Shulman *et al.* 1999; Barney and Graziano, 2003].

Difluprednate (Durezol®, Alcon), which is indicated for the treatment of postoperative inflammation and pain, has been shown to reduce both provocation-induced early phase itching, and the late-phase ocular itching and hyperemia associated with SAC [Leonardi *et al.* 2002].

### *Immunomodulators*

Two topical immunomodulatory agents have been evaluated in multiple studies for treatment of the vision-threatening and severe VKC and AKC: cyclosporine A (Restasis®, Allergan) and tacrolimus (Protopic®, Astellas Pharma, Tokyo, Japan) [Erdinest and Solomon, 2014]. The topical ointment cyclosporine A, indicated for dry-eye syndrome, apparently modulates mast-cell activity by reducing calcium influx, degranulation, and cytokine gene expression [Whitcup *et al.* 1996]. In a notable Japanese study of 594 patients with VKC and AKC, cyclosporine A 0.1% significantly decreased all objective and subjective scores, including itching. Moreover, 44.4% of patients with VKC and 21.9% of patients with AKC ceased therapy because their symptoms resolved, and approximately 30% of steroid users were able to discontinue concomitant topical steroid use. Eye irritation was the most common adverse event (4.4%) and all infectious incidents ($n$ = 10) occurred in subjects undergoing concomitant steroid use [Ebihara *et al.* 2009].

Cyclosporine A 1% appears to be the minimal effective concentration for the treatment of severe VKC and perhaps AKC [Bleik and Tabbara, 1991; Gupta and Sahu, 2001; Pucci *et al.* 2002, 2010; Spadavecchia *et al.* 2006; Erdinest and Solomon, 2014; Wu *et al.* 2014]. The low dose (cyclosporine A 0.05%) had mixed results in the alleviation of ocular itching and/or other symptoms of chronic AC [Akpek *et al.* 2004; Kosrirukvongs and Luengchaichawange, 2004; Daniell *et al.* 2006; Keklikci *et al.* 2008; Erdinest and Solomon, 2014; Wu *et al.* 2014].

Tacrolimus, with a potency 100-fold that of cyclosporine, blocks cellular steroid receptors, inhibiting mediator release from mast cells and, thereby, suppressing T-cell activation and consequent B-cell proliferation (late-phase allergic responses) [Sawada *et al.* 1987; Erdinest and Solomon, 2014]. Although the tacrolimus 0.1% and 0.005% formulations proved efficacious, the tacrolimus 0.3% formulation apparently offers the optimal efficacy in treatment of ocular itching and improvement across all other subjective and objective measures [Attas-Fox *et al.* 2008; Zribi *et al.* 2009; Ohashi *et al.* 2010; Tam *et al.* 2010; Kheirkhah *et al.* 2011]. In one study, tacrolimus had greater efficacy than cyclosporine A in the treatment of ocular itching and other signs and symptoms of allergic eye diseases, particularly in refractory VKC [Miyazaki *et al.* 2008; Ohashi *et al.* 2010; Kheirkhah *et al.* 2011; Al-Amri, 2014].

## New dual-action agents

The dual-action topical antihistamines are now the forefront of effective therapy against the benign forms of AC (SAC and PAC). These multimodal agents combine the actions of histamine-receptor antagonists, superior to previous generation antihistamines, coupled with the actions of mast-cell stabilizers. These collective mechanisms provide immediate and sustained relief during both early and late-phase ocular allergic reactions [Namdar and Valdez, 2011; Williams *et al.* 2011].

### *Olopatadine – the historical gold standard*

The first dual-action topical agent to change the therapeutic paradigm was olopatadine 0.1% (Patanol®, Alcon), approved by the FDA in 1996 for treatment of the signs and symptoms of AC. It is highly selective for the H1-histamine receptor, lacking interaction with the histamine H2 and H3, adrenergic, dopaminergic, and muscarinic receptors [Nonaka *et al.* 1993; Sharif *et al.* 1996]. Olopatadine is apparently anti-inflammatory as well, and has been shown to inhibit the release of leukotrienes, adhesion molecules, and cytokines [Miki *et al.* 1996; Yanni *et al.* 1999; Cook *et al.* 2000, 2001; Kaliner *et al.* 2010].

In numerable comparative studies, olopatadine demonstrated superiority to archetypical agents of

all previous generations for ocular itching relief, for example, the second-generation topical and oral antihistamines (fexofenadine, levocabastine, and loratadine) [Abelson and Welch, 2000; Lanier *et al.* 2002; Abelson 2004], the mast-cell stabilizers (cromolyn sodium and nedocromil sodium) [Butrus and Wun, 2000; Katelaris *et al.* 2002], the NSAID ketorolac [Deschenes *et al.* 1999; Yaylali *et al.* 2003], and the corticosteroids (fluorometholone and loteprednol) [Berdy *et al.* 2002; Borazan *et al.* 2009]. Also, in comfort studies, olopatadine was found more comfortable than levocabastine, ketorolac, and nedocromil sodium [Deschenes *et al.* 1999; Katelaris *et al.* 2002; Abelson 2004].

Olopatadine 0.1% was the first topical AC agent approved for twice-daily dosing in contrast to the second-generation antihistamines which, in their time, had advanced convenience and adherence with four times a day dosing [Abelson, 2004; Leonardi and Quintieri, 2010]. Subsequently, a once-daily formulation of olopatadine 0.2% (Pataday®) became available, which provided comparable efficacy and improved patient satisfaction [Abelson *et al.* 2004b, 2007; Kaliner *et al.* 2010]. Olopatadine 0.2% is approved specifically for inhibition of ocular itching rather than the signs and symptoms of AC.

In February 2015, olopatadine 0.7% (Pazeo™, Alcon) was introduced on to the market as the latest generation of this molecule, also for once-daily dosing, but with efficacy for ocular itching demonstrated to 24 h instead of the 18 h duration established for 0.2% olopatadine [Novartis, 2015].

### *Ketotifen – the first challenger*

Approved in 1999, ketotifen (Zaditor®, Alcon) was the second dual-action agent on the market. Ketotifen was shown to be inferior to olopatadine 0.1% for the treatment of itching, hyperemia, and tearing in a 14-day seasonal trial [Aguilar, 2000]. In a later study, preservative-free ketotifen was shown to be of comparable efficacy to olopatadine 0.1% [Mortemousque *et al.* 2014]. Olopatadine also scored higher than ketotifen in comfort scores [Artal *et al.* 2000; Mortemousque *et al.* 2014].

### *Azelastine – less favored*

Approved in 2000, azelastine (Optivar®, Meda Pharmaceuticals, Bishop's Stortford, UK) fared poorly in direct comparison with olopatadine for itching secondary to AC. Patients in two studies subjectively rated olopatadine 0.2% more comfortable than azelastine by a ratio of 4:1, as well as subjectively scoring olopatadine better in the alleviation of itching, redness, tearing, and swelling, although only swelling scores were statistically significant, olopatadine 01% also scored better in tolerability than azelastine [Spangler *et al.* 2001; D'Arienzo and Granet, 2001; Scoper *et al.* 2007; Epstein *et al.* 2009].

### *Epinastine – short of promise*

Approved in 2003, epinastine (Elestat®, Allergan) seemed a drug with much promise: it had high selectivity for histamine H1- and H2-receptors, providing downregulation of inflammatory mediators, and seemed virtually free of adverse reactions. Its pivotal evaluations included an environmental study; patients found it more tolerable than azelastine and ketotifen, and it had a prolonged duration of effect, perhaps up to 8 h or 10 h [Friedlaender *et al.* 2000, 2004; Abelson *et al.* 2004; Abelson, 1990a; Whitcup *et al.* 2004; Mah *et al.* 2007; Borazan *et al.* 2009; La Rosa *et al.* 2013; Fujishima *et al.* 2014]. However, the drug failed to demonstrate superiority to olopatadine in preventing ocular itching and hyperemia, although epinastine did demonstrate noninferiority to olopatadine in a more recent study [Lanier *et al.* 2002; Finegold *et al.* 2006; Mah *et al.* 2007; Fukushima and Ebihara, 2014].

### *Bepotastine – an unfortunate latecomer*

Bepotastine (Bepreve®, Bausch and Lomb), approved in 2009, also seemed to have great potential. In provocation tests, its inhibition of the late-stage reaction granted bepotastine an 8 h duration of efficacy [Abelson *et al.* 2009; Macejko *et al.* 2010; Bergmann *et al.* 2014]. In one study, a 'sizable' proportion reported complete relief from itching at 16 h post-instillation [Bergmann *et al.* 2014]. Notably, the efficacy of bepotastine for ocular itching in subjects with SAC had been demonstrated in an environmental trial using twice-daily dosing [Carr *et al.* 2013]. Comparison trials involving bepotastine seem lacking, and the advent of alcaftadine 1 year later changed the competitive landscape.

### *Alcaftadine – a new forefront of efficacy*

The most recent novel dual-action agent available on the market is alcaftadine (Lastacaft®, Allergan), approved in 2010, and which has several distinguishing properties that differentiate it from all

predecessors. First, the affinity alcaftadine has for histamine H1- and H2-receptors is 10 times greater than that of olopatadine [Gallois-Bernos and Thurmond, 2012]. Alcaftadine also has a moderate affinity for H4-receptors [Bohets *et al.* 2011], which are expressed on mast cells, leukocytes, and CD4+ cells, evidently granting alcaftadine its ability to inhibit eosinophil recruitment, the late-stage component [Namdar and Valdez, 2011]. Comparatively, olopatadine lacks any affinity for the H4-receptor [Sharif *et al.* 1996].

The preceding H1-antagonists seem to lack the ability of alcaftadine to inhibit eosinophil infiltration, activity that might contribute to alcaftadine's prolonged efficacy, which allows for once-daily dosing [Namdar and Valdez, 2011; Williams *et al.* 2011; Gallois-Bernos and Thurmond, 2012]. Alcaftadine is well tolerated, with the most frequent ocular adverse events, occurring in less than 4% of the population, including burning upon instillation, redness, and pruritus [Namdar and Valdez, 2011].

Alcaftadine acts as a conjunctival epithelial stabilizer, a unique property. The tight junctions of the conjunctival epithelium protect the ocular surface, serving as physical barriers to allergens and organisms. Numerous common allergens possess proteolytic enzymes that degrade the junctional proteins [Namdar and Valdez, 2011]. Within diseased conjunctiva, these junctions lose integrity, allowing allergen permeation. In a murine model, alcaftadine stabilized and protected these junctions whereas olopatadine did not [Ono and Lane, 2011].

Alcaftadine also outperformed olopatadine clinically in a series of evaluations. In two once-daily dosing trials, alcaftadine 0.25% demonstrated greater efficacy in prevention of ocular itching than olopatadine 0.2% at 3 min post-challenge and every time point up to 16 h post-instillation [Ackerman *et al.* 2013; McLaurin *et al.* 2014]. Alcaftadine was also the only active treatment that provided statistically significant relief of chemosis at every time point at the 24 h post-instillation visit [Ackerman *et al.* 2013]. In a third trial, alcaftadine had significantly greater efficacy 16 h post-instillation [Greiner *et al.* 2011].

## The future of AC treatment

Undoubtedly, new pharmacological agents and new treatment paradigms will emerge as time progresses. For example, the new topical corticosteroid, mapracorat, is in the developmental pipeline. Mapracorat, currently undergoing phase II clinical evaluation, potentially retains the potency of the old guard yet with a more favorable safety profile. Compared with the classical glucocorticoid dexamethasone, mapracorat induces a significantly milder increase in IOP (Baiula and Spampinato, 2014; NIH, 2015a, 2015b, 2015c]

Certainly eosinophil adhesion and accumulation have been the focus of many new allergic targets. Several small molecule antagonists of α4B1 integrin have been developed and tested in animal models of allergy [Baiula *et al.* 2012]. Monoclonal antibodies that inhibit ICAM-1 binding have been explored in various inflammatory disorders. The second- and third-generation antihistamines have been shown to inhibit ICAM-mediated eosinophil adhesion in AC. Glucocorticoids including mapracorat are also potent inhibitors of eosinophil adhesion [Baiula *et al.* 2012].

Another class of agents undergoing further development is the leukotriene receptor antagonist. Studies are currently focused on montelukast, and a recent meta-analysis concluded that montelukast was more effective in alleviating allergic eye disease than placebo, but less effective than oral antihistamines. The current body of literature might warrant additional clinical research into the efficacy of montelukast and oral histamine combinations for ocular signs and symptoms of allergy [Gane and Buckley, 2013].

In the domain of immunomodulatory agents, in addition to cyclosporine A and tacrolimus, several other agents have also shown efficacy in the treatment of ocular immune-mediated diseases such as mycophenolate mofetil, leflunomide, rapamycin (sirolimus), glatiramer, laquinimod, and infliximab; however, the lipophilic nature and low water solubility of immunomodulatory agents has imposed limits on drug delivery owing to the multilayer structure of the cornea [Bertelmann and Pleyer, 2004; Mishra *et al.* 2011]. The antibodies of infliximab and daclizumab have also demonstrated potential efficacy in the alleviation of conjunctivitis symptomology [De Carvalho *et al.* 2009].

A different approach to immunomodulation is subcutaneous and sublingual immunotherapy, that is, allergen exposure to desensitize the

immune system to a specific allergen. Large-scale trials are underway in the USA for grass and ragweed allergies. One drawback to the immunotherapy research is the limited focus on ocular symptoms in large-scale trials, although the indication being sought is in fact allergic rhinoconjunctivitis. Ocular itching does not currently serve as a parameter in these studies [Mishra *et al.* 2011]. One experimental study explored the possibility of oral immunotherapy for Japanese cedar allergic conjunctivitis through the addition in transgenic rice of deconstructed cedar antigen [Fukuda *et al.* 2015]. This approach is specific to a single allergen, and might best be reserved for patients with predominantly single allergen sensitivities. It is hoped that in future clinical trials of immunotherapy, ocular signs and symptoms will be assessed in accordance with the broad indication sought, and the potential that attenuation of whole body sensitivity to allergen provides.

## Conclusion

Undoubtedly, the dual-action agents represent the forefront of efficacy in the treatment of ocular itching caused by allergic conjunctivitis with the newest agent, alcaftadine, foremost among them. Nevertheless, alcaftadine may be challenged in gaining ascendancy in the marketplace, given the historical dominance of olopatadine, combined with the introduction of the olopatadine 0.7% formulation.

In terms of patient care, the greatest problem may be the education of both patients and primary care physicians who, along with ophthalmologists, demarcate the front line of treatment intervention versus AC. Given that the habitual use of legacy medications persists in the face of evolved options having greater efficacy against ocular itching, outreach programs to self-medicating patients and primary care physicians may have the greatest impact on alleviating the suffering and morbidity consequent to allergic conjunctivitis.

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