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Efficacy and Tolerability of Newer Antihistamines in the Treatment of Allergic Conjunctivitis

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Abstract

Treatment for allergic conjunctivitis has markedly expanded in recent years, providing opportunities for more focused therapy, but often leaving both physicians and patients confused over the variety of options. As monotherapy, oral antihistamines are an excellent choice when attempting to control multiple early-phase, and some late-phase, allergic symptoms in the eyes, nose and pharynx. Unfortunately, despite their efficacy in relief of allergic symptoms, systemic antihistamines may result in unwanted adverse effects, such as drowsiness and dry mouth. Newer second-generation antihistamines (cetirizine, fexofenadine, loratadine and desloratadine) are preferred over older first-generation antihistamines in order to avoid the sedative and anticholinergic effects that are associated with first-generation agents. When the allergic symptom or complaint, such as ocular pruritus, is isolated, focused therapy with topical (ophthalmic) antihista-

mines is often efficacious and clearly superior to systemic antihistamines, either as monotherapy or in conjunction with an oral or intranasal agent.

Topical antihistaminic agents not only provide faster and superior relief than systemic antihistamines, but they may also possess a longer duration of action than other classes including vasoconstrictors, pure mast cell stabilisers, NSAIDs and corticosteroids. Many antihistamines have anti-inflammatory properties as well. Some of this anti-inflammatory effect seen with 'pure' antihistamines (levocabastine and emedastine) may be directly attributed to the blocking of the histamine receptor that has been shown to downregulate intercellular adhesion molecule-1 expression and, in turn, limit chemotaxis of inflammatory cells. Some topical multiple-action histamine H_1-receptor antagonists (olopatadine, ketotifen, azelastine and epinastine) have been shown to prevent activation of neutrophils, eosinophils and macrophages, or inhibit release of leukotrienes, platelet-activating factors and other inflammatory mediators. Topical vasoconstrictor agents provide rapid relief, especially for redness; however, the relief is often short-lived, and overuse of vasoconstrictors may lead to rebound hyperaemia and irritation. Another class of topical agents, mast cell stabilisers (sodium cromoglicate [cromolyn sodium], nedocromil and lodoxamide), may be considered; however, they generally have a much slower onset of action. The efficacy of mast cell stabilisers may be attributed to anti-inflammatory properties in addition to mast cell stabilisation. In the class of topical NSAIDs, ketorolac has been promoted for ocular itching but has been found to be inferior for relief of allergic conjunctivitis when compared with olopatadine and emedastine. Lastly, topical corticosteroids may be considered for severe seasonal ocular allergy symptoms, although long-term use should be avoided because of risks of ocular adverse effects, including glaucoma and cataract formation.

Since the availability of second-generation antihistamines, with their low- or non-sedating and anticholinergic profiles, the treatment armamentarium against allergic 'rhinoconjunctivitis' has markedly expanded. This can be attributed to the maintenance of the efficacy of previous generation of antihistamines, coupled with a more favourable safety profile and fewer adverse effects. Common adverse effects of first-generation histamine H_1-receptor antagonists include sedation and anticholinergic effects, such as dry mouth, dry eyes, blurred vision and urinary retention.

First- and second-generation antihistamines have been studied in detail with respect to the treatment of allergic rhinitis, but only limited data have focused on the treatment efficacy of antihistamines on the ocular symptoms of allergic 'conjunctivorhinitis'. Ocular signs and symptoms, including itching, tearing, redness and chemosis, are often treated collectively within the constellation of allergic rhinoconjunctivitis, commonly as a single domain referred to as the 'total symptom score' in many clinical trials, and have only recently been relegated to an area of concentrated research.

Orally administered second-generation antihistamines have provided effective relief of nasal symptoms, with clear dominance in the total symptom score and, in many instances, reaching significance in the ocular component of the total symptom score. These antihistamines significantly dampen or block the early-phase and some of the features of the late-phase response including swelling and redness. The available oral second-generation antihistamines in the US include acrivastine, cetirizine, fexofenadine, loratadine and desloratadine. Other second-genera-

tion agents not currently available in the US include ebastine, levocetirizine and mizolastine.

A large array of new topical ocular agents are available for use in patients who primarily complain of ocular allergy symptoms or as a supplement to oral agents. Topical agents typically provide faster relief of ocular symptoms compared with oral agents. With direct administration a higher concentration of the medication can be delivered to the conjunctivae, thus becoming an ideal mode of treatment.

Topical agents typically have multiple mechanisms of action, including antihistaminic, mast cell stabilising and anti-inflammatory properties. The relative 'pure' antihistaminic agents are levocabastine and emedastine, although premedicating patients with levocabastine has been shown to also have some effect on the late-phase ocular allergy response.[1] The antihistaminic and mast cell stabiliser combinations are ketotifen, epinastine, azelastine and olopatadine. The other classes of topical agents include mast cell stabilisers, NSAIDs, corticosteroids and immunomodulatory agents.

By understanding the mechanisms of ocular allergy and the actions of medications, we will be better able to understand and target areas for treatment. The ocular conjunctiva is a mucosal surface that is highly exposed to environmental allergens and is often the first site of contact with our immune system, generating an ocular allergic reaction. After antigen exposure, mast cell degranulation occurs with immediate release of pre-formed and newly synthesised mediators. Histamine is the primary preformed mediator responsible for the typical early-phase reactions, triggering itching, redness and swelling. Newly synthesised mediators, including cysteinyl leukotrienes and prostaglandins, are associated with increased mucus secretion and cellular infiltration, in addition to the symptoms seen in the acute-phase response. Prostaglanin D_2 is the main prostaglandin released and has been shown to cause redness, chemosis and mucus discharge when applied to the eye.[2] The leukotrienes LTC4, LTD4 and LTE4 have been identified in tears after conjunctival challenge and act synergistically with prostaglandin D_2 to enhance vascular permeability.[3]

The mast cells also synthesise and release cytokines, including interleukin (IL)-4, IL-5, platelet-activating factor and tumour necrosis factor (TNF). The release of cytokines, chemokines and growth factors triggers a cascade of inflammatory events, including the increased expression of adhesion molecules, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule-1, on the surface of epithelial cells, which leads to a late-phase response with recruitment of eosinophils and neutrophils. This cellular inflammation is responsible for adding to the ocular injury. Major basic protein and other eosinophil mediators result in epithelial desquamation and injury.

In the normal conjunctiva, mast cells are normally present in the substantia propria, below the basement membrane in a concentration of 5000–6000 mast cells/mm^3.[4] In allergic conjunctivitis, mast cells start to increase in number in the substantia propria and with increased chronicity of ocular inflammation, the mast cells eventually infiltrate the epithelium. A single mast cell detected in the conjunctival epithelium is diagnostic of allergic conjunctivitis.[5] Conjunctival mast cells belong to the connective-type class of mast cells (MCTC), containing chymase and tryptase, which predominates in skin and intestinal submucosa. The other class of mast cells (MCT) are the mucosal mast cells, containing tryptase, and are predominantly found in intestinal mucosa and lung alveolar wall.

In addition to specifically blocking H_1 receptors, many of the available antihistamines also prevent histamine production, bind to adrenergic, cholinergic and muscarinic receptors, and inhibit mediator release from mast cells, while others inhibit different components of the allergic inflammatory cascade. Even 'pure' antihistamines have some anti-inflammatory action. Inactivation of H_1 receptors results in decreased levels of nuclear factor-$\kappa\beta$, a transcription factor important in the regulation of cytokine and ICAM-1 expression.

ICAM-1 expression plays a critical role in the allergic cascade. ICAM-1 interactions with the β_2

Table I. Comparison of receptor binding affinities (dissociation constant of an inhibitor [K_i][a]) of second-generation antihistamines

	H_1 receptor (nM)	H_2 receptor (nM)	H_3 receptor (nM)	Muscarinic receptor (nM)
Ketotifen	1.3[10]	1115[10]	2277[10]	204[11]
Emedastine	1.3[10]	49 067[10]	12 430[10]	NA
Desloratadine	4[12]	NA	NA	21 (M_2)[12]
Cetirizine	6.3[13]	NA	NA	<100 000[11]
Azelastine	6.8[14]	1.61 (IC_{50})[b,c]	71.3 (IC_{50})[b,c]	457[11]
Epinastine	9.8 (IC_{50}[b])[16]	4030 (IC_{50}[b])[16]	NA	NA
Diphenhydramine	12.5[17]	1600[17]	25 000[17]	280[18]
Olopatadine	31.6[17]	100 000[17]	79 400[17]	NA
Loratadine	35[19]	NA	NA	NA
Levocabastine	56.0[10]	23 500[10]	4597[10]	NA
Fexofenadine	83[12]	NA	NA	50 000 (M_2)[12]

a K_i is the dissociation constant of an inhibitor based on the Cheng-Prussof equation, $K_i = IC_{50}/(1 + L/K_d)$, such that a lower value denotes higher binding affinity, where L is the radioligand concentration and K_d is the dissociation constant.

b Affinity expressed as IC_{50}.

c Data taken from the US FDA monograph.[15]

IC_{50} = concentration of drug needed to produce 50% inhibition of the receptor binding; **NA** = data not available.

integrins, lymphocyte function-associated antigen-1 and macrophage antigen-1, on the surface of leucocytes are important for leucocyte attachment to epithelial and endothelial cells. After allergen exposure, conjunctival cells are induced to express ICAM-1, thus facilitating the recruitment of inflammatory cells. *In vivo* models have demonstrated this rise in ICAM-1 expression after conjunctival antigen challenge.[6] Several H_1-receptor antagonists (azelastine, cetirizine, fexofenadine, levocabastine) have been demonstrated to downregulate ICAM-1 expression.[7] This antihistaminic action has been observed to be a direct effect *in vitro* on epithelial cells and fibroblasts.[8] A reduction in ICAM-1 expression can account for some of the anti-inflammatory effects of second-generation antihistamines.

It is important to understand the available treatment alternatives and to explore the best treatment regimen for each patient. This article reviews the current newer antihistamines available, and explores their efficacy and tolerability with respect to their modalities of treatment, whether topical or systemic or a combination of both for the treatment of ocular allergy.

1. Oral Agents

When compared with first-generation antihistamines, newer second-generation antihistamines bind much more selectively to peripheral H_1 receptors (table I). This is advantageous because the second-generation antihistamines have a lower binding affinity for the cholinergic and α-adrenergic receptor sites, which account for many of the adverse effects of antihistamines, including CNS depression, dry mouth, blurred vision and tachycardia. The benefits of oral H_1-receptor antagonists on alleviating ocular itching, tearing and redness have been clearly demonstrated. On the other hand, the binding affinity to H_2 receptors appears to be quite variable, when comparing first- and second-generation antihistamines (table I). There are multiple studies examining the effect of H_2-receptor antagonists on vasodilation, although only limited studies exist that infer the effect on ocular vasodilation and the development of erythema and swelling.[9] A summary of pharmacokinetic properties and recommended dosages of oral second-generation antihistamines is given in table II.

1.1 Cetirizine

Cetirizine, a piperazine derivative and carboxylated metabolite of hydroxyzine, is a potent

H_1-receptor antagonist, classified as low sedating. A few conjunctival provocation studies have demonstrated its efficacy in the treatment of allergic conjunctivitis.[25-27] Cetirizine is rapidly absorbed and achieves its peak plasma concentration in 1.0 ± 0.5 hours.[20] Typically, second-generation oral antihistamines achieve peak plasma concentrations within 1–3 hours after administration.

In a study that investigated the tear and plasma concentrations of cetirizine after a single oral dose, the maximum mean plasma concentration was achieved at 30 minutes, whereas the maximum mean tear fluid concentration was achieved later at 90 minutes.[28] This suggests that ocular symptoms may respond more slowly to systemic treatment as there is a delay in achieving a therapeutic drug concentration in the tear fluid or conjunctivae. However, cetirizine was found to reach plateau concentrations in tear fluid similar to that of serum levels. At 60 and 120 minutes after a single oral dose, the cetirizine concentration in tear fluid was 98% and 92% of the mean maximum concentration, respectively. Thus, oral administration of cetirizine may be a suitable route for achieving relief of ocular allergies, although specific studies focusing on ocular symptoms as the primary endpoint are lacking.

In addition to selective H_1-receptor antagonism, cetirizine inhibits eosinophil chemotaxis during the allergic response and can, thus, blunt the late-phase reaction.[29] In the conjunctival challenge study by Ciprandi et al.,[6] cetirizine was found to have a protective effect on the clinical features and cellular response of the early- and late-phase reactions. Clinical improvements occurred with itching, hyperaemia, lacrimation and eyelid swelling in early-phase (30 minutes) and late-phase (24 hours) reactions after conjunctival challenge. Evaluation of conjunctival scrapings revealed decreased eosinophils and neutrophils in early- and late-phase reactions. Furthermore, ICAM-1/CD54 expression was significantly reduced by cetirizine in both the early- and late-phase reactions compared with placebo.

1.2 Fexofenadine

Fexofenadine, the active carboxylic acid metabolite of terfenadine, is a potent H_1-receptor antagonist that does not affect the QT interval like its predecessor. Fexofenadine also has proven anti-inflammatory activity and has been shown to inhibit a number of mediators at clinically relevant concentrations, including *in vitro* inhibition of ICAM-1 expression on conjunctival and nasal epithelial cells.[30] Multiple studies have demonstrated the efficacy of fexofenadine in the treatment of the symptoms of seasonal allergic rhinitis, including ocular symptoms.[31-35] In comparison studies, fexofenadine was significantly more effective than loratadine in relieving ocular symptoms and nasal congestion at 24 hours ($p \leq 0.05$ for both).[36] Fexofenadine was found to be comparable with cetirizine in the treat-

Table II. Oral second-generation histamine H_1-receptor antagonists

Drug/preparations	Recommended dosage	t_{max} (h)[20]	$t_{1/2}$ (h)[20]	Common adverse effects
Cetirizine tabs: 5 and 10mg syrup: 1 mg/mL chewable tabs: 5 and 10mg	≥6y: 5 or 10 mg/day 2–5y: 2.5mg (½ tsp) syrup daily to maximum 5 mg/day 6mo to <2y: 2.5mg (½ tsp) syrup daily to maximum 5 mg/day	1.0 ± 0.5	6.5–10 (mean 8.3)	Somnolence: 11% (5mg), 14% (10mg); fatigue (5.9%); dry mouth (5%)[21]
Fexofenadine tabs: 30, 60 and 180mg	≥12y: 180 mg/day or 60mg twice daily 6–11y: 30mg twice daily	1–3	14.4	Headache (7.2–10.6%)[22]
Loratadine tabs: 10mg syrup: 1 mg/mL	≥6y: 10 mg/day 2–5y: 5mg (1 tsp) daily	1.2 ± 0.3	7.8 ± 4.2	≥12y: headache (12%), somnolence (8%), fatigue (4%), dry mouth (3%) 6–12y: nervousness (4%), wheezing (4%), fatigue (3%)[23]
Desloratadine tabs: 5mg	≥12y: 5 mg/day	NA	21–31	Pharyngitis (4.1%), dry mouth (3%)[24]

NA = not applicable; **$t_{1/2}$** = half-life; **tabs** = tablets; **t_{max}** = time to maximum concentration; **tsp** = teaspoon.

ment of seasonal allergic rhinitis, but the incidence of drowsiness or fatigue was greater with cetirizine (9%) than with fexofenadine (4%, p = 0.02) or with placebo (4%, p = 0.07).[37] Additionally, combination therapy with fexofenadine and pseudoephedrine was significantly more effective than fexofenadine or pseudoephedrine alone in relieving the symptoms of seasonal allergic rhinitis, including ocular signs and symptoms of redness, pruritus and wateriness (p = 0.0006).[38] In several studies, fexofenadine was not found to have an adverse impact on cognitive or psychomotor function.[39-43]

1.3 Loratadine

Loratadine is a piperidine derivative that exerts a protective effect on the early- and late-phase reactions of conjunctival allergic reactions.[44,45] In a double-blind, randomised, placebo-controlled, parallel-group study by Ciprandi et al.,[44] patients with a history of seasonal allergic rhinoconjunctivitis received loratadine 10 mg/day or placebo daily for 7 days prior to allergen-specific conjunctival provocation. Loratadine produced a significant reduction in conjunctival symptom severity at 30 minutes and 6 hours, as well as a reduction in inflammatory cell infiltration by conjunctival scrapings at the same timepoints ($p < 0.01$ for both). In a study comparing fexofenadine/pseudoephedrine versus loratadine/montelukast combination, fexofenadine/pseudoephedrine had a larger impact on ocular symptoms in a quality-of-life assessment than did the loratadine/montelukast combination, which appeared to be equivalent to placebo.[46] In a comparative study, patients with seasonal allergic rhinitis showed significantly greater relief in eye symptoms with loratadine as compared with beclometasone nasal corticosteroid spray.[47] Despite its efficacy in allergic conjunctivitis, loratadine may still produce some minimal ocular drying by decreasing tear film.[48,49]

1.4 Desloratadine

Desloratadine, a non-sedating H_1-receptor antagonist, is the principal metabolite of loratadine. It has been found to reduce the symptoms of perennial allergic rhinitis, including ocular itching and tearing, as early as the first dose, and for the duration of the 4-week study.[50] In two placebo-controlled studies, published together, the effectiveness of desloratadine compared with placebo, was conducted in the spring and autumn, respectively.[51] In the first study of 346 subjects (172 in desloratadine and 174 in placebo group) during the spring tree pollen season, the ocular symptom scores for desloratadine improved by 28% compared with 9% for placebo. In the smaller autumn allergy season study (n = 328), the difference from placebo was less (average of 31% vs 19% for individual ocular symptoms), but still statistically significant for itching and redness ($p \leq 0.04$). Although clearly effective for ocular symptoms, desloratadine was found to be inferior in a comparison with the topical agent, ketotifen.[52]

2. Topical Antihistaminic Agents

Systemic antihistamines have the advantage of controlling a variety of nasal, pharyngeal and ocular symptoms and, thus, may be the preferred treatment when the symptoms are mild enough for monotherapy. However, the more direct approach of topical administration has been shown to be more efficacious for the exclusive treatment of ocular symptoms. Many studies utilising the conjunctival antigen challenge model have demonstrated that topical agents are indeed superior agents, particularly when used in conjunction with other treatment modalities. Topical antihistaminic agents provide rapid relief of ocular symptoms compared with systemic antihistamines. Topical antihistaminic agents also have fewer adverse effects than systemic antihistamines because of the lower doses required to penetrate the conjunctivae and the negligible serum levels from topical use.

The two classes of topical agents that have antihistaminic properties are the ‘pure’ antihistamine group and the ‘multiple-action’ group with combined antihistamine activity, mast cell stabilisation and pro-inflammatory mediator inhibitory action (table III). Other classes involved in the treatment of ocular allergies include vasoconstrictors, pure mast cell stabilisers, NSAIDs and corticosteroids. Vaso-

Table III. Topical (ophthalmic) antihistamines for allergic conjunctivitis

Drug	Recommended dosage	Most common adverse effects
'Pure' antihistamines		
Levocabastine	≥12y: 1 drop per eye 2–4 times daily	Ocular stinging or burning (29%), headache (5%)[53]
'Multiple-action' topical agents		
Olopatadine	≥3y: 1–2 drops twice daily, 6–8h intervals	Headache (7%)[54]
Emedastine	≥3y: 1 drop four times daily	Headache (11%)
Ketotifen	≥3y: 1 drop twice daily, 8–12h intervals	Conjunctival injection (7%), headache (1.5%)[55]
Azelastine	≥3y: 1 drop twice daily	Ocular burning (~30%), headache (~15%), bitter taste (~10%)[56]
Epinastine	≥3y: 1 drop twice daily	Upper respiratory tract infection/cold symptoms (10%)[57]

constrictors are sympathomimetic agents that decrease vascular congestion and eyelid oedema via α-receptor stimulation. They have no effect on diminishing the allergic inflammatory response.

Topical vasoconstrictors, as monotherapy or combination therapy with an antihistamine, are widely available as over-the-counter treatments for ocular allergy and are effective in reducing hyperaemia. Combination agents, such as naphazoline/pheniramine, are effective short-term agents with rapid onsets of action. However, vasoconstrictor agents used alone may have no effect on ocular pruritus. Additionally, topical vasoconstrictors are only recommended for short-term use because of potential adverse effects of rebound conjunctival hyperaemia with long-term use.[58]

3. 'Pure' Antihistamine Topical Agents

3.1 Levocabastine

Levocabastine, a cyclohexyl piperidine derivative, is a selective H_1-receptor antagonist that has been shown to be more effective than placebo in the topical treatment of allergic conjunctivitis.[59] In addition to its antihistaminic activity, levocabastine has been shown to downregulate ICAM-1 expression.[1,60] The drug has been shown to be more effective than topical sodium cromoglicate (cromolyn sodium) for the treatment of seasonal allergic 'conjunctivorhinitis'.[61,62] When compared with lodoxamide, a mast cell stabiliser, levocabastine has been shown to be as efficacious and well tolerated, and possessing a faster onset of action.[63] In another conjunctival provocation study, a single drop of levocabastine was significantly more effective than 2 weeks of pretreatment with topical sodium cromoglicate in inhibiting ocular pruritus, hyperaemia, eyelid swelling, chemosis and tearing ($p < 0.05$).[64] In a multicentre study by the Swedish GP Allergy Team,[65] 95 adult patients with birch-pollen seasonal allergic rhinoconjunctivitis were randomised during a 5-week period to receive a combination regimen of either ocular levocabastine/intranasal levocabastine/oral placebo or ocular placebo/intranasal placebo/oral loratadine. The mean daily symptom severity scores for ocular and nasal symptoms were comparable in the two groups. Eighty-six percent of levocabastine-treated patients considered the therapy to be good or excellent, as compared with 77% of the loratadine-treated patients. The suppression of the early-phase reaction does not preclude the development of a late-phase reaction.[66]

4. 'Multiple-Action' Topical Agents

4.1 Olopatadine

Olopatadine is a long-acting multiple-action topical agent with mast cell stabilising and antihistaminic properties. Olopatadine has been shown to be effective against ocular pruritus for up to 8 hours.[67] A single drop of olopatadine was shown to be more efficacious than a 2-week load with nedocromil, a mast cell stabiliser, in a conjunctival antigen challenge model.[68] In another conjunctival antigen challenge study that compared topical and oral delivery of antihistamines, lower ocular itching scores were seen in patients who received topical

olopatadine when compared with oral administration of loratadine at 3, 7 and 10 minutes after conjunctival antigen challenge.[69]

In a conjunctival antigen challenge study, olopatadine was found to reduce tear histamine levels, cellular infiltration and ICAM-1 expression after conjunctival antigen challenge.[70] Tear cytology demonstrated a significant reduction in neutrophils and total cells at 30 minutes, and a significant reduction in eosinophils, neutrophils, lymphocytes and total cells at 5 hours after conjunctival antigen challenge in eyes pretreated with olopatadine. Olopatadine also significantly reduced ICAM-1 expression at 30 minutes and 5 hours post-challenge. The inhibition of mast cell-derived mediators correlated with a reduction of ocular pruritus and redness. Olopatadine has also been demonstrated *in vitro* to inhibit release of TNFα from human conjunctival mast cells and, thus, blocking upregulation of ICAM-1.[71,72]

Concomitant use of fluticasone propionate and topical olopatadine produced significantly greater improvements in ocular itching at 3 and 7 minutes after conjunctival antigen challenge compared with fluticasone propionate and oral fexofenadine.[73] It would be safe to conclude that topical administration of antihistamine was more effective in the control of ocular pruritus than an oral antihistamine, especially as it has been demonstrated that oral medications may take over an hour to achieve their maximum concentration in tear fluid. In addition, both treatment groups produced comparable improvements in nasal symptoms.

4.2 Ketotifen

Ketotifen, a benzocycloheptathiophene, is a noncompetitive H_1-receptor antagonist that stabilises mast cells, inhibits platelet-activating factor and acts as an eosinophil inhibitor. It has no apparent effect on adrenergic, dopaminergic or serotonin 5-HT receptors. Ketotifen has demonstrated direct inhibitory effect on eosinophil oxidative metabolism.[74] In a dose-dependent manner, ketotifen *in vitro* was found to inhibit eosinophil chemotaxis.[75]

Ketotifen was found to have statistically superior effect on ocular itching and hyperaemia when compared with placebo ($p < 0.001$ and $p < 0.05$, respectively), and benefits were seen within 15 minutes of treatment and lasted for at least 8 hours.[76] A single dose of ketotifen was found to be superior to 2 weeks of topical sodium cromoglicate in alleviating ocular itching, tearing and redness in the conjunctival antigen challenge model.[77] In a 3-week parallel-group study of ketotifen and olopatadine in 66 patients with seasonal allergic conjunctivitis, ketotifen was found to have higher global efficacy ratings and to reduce the severity of hyperaemia and itching more than olopatadine.[78] Both agents had comparable comfort ratings. In contrast, in a 2-week study of 80 patients with symptomatic allergic conjunctivitis, ketotifen was less efficacious than olopatadine and was found to trigger mild symptoms, such as stinging, in 23% of patients.[79] In a 6-week study in patients ≥3 years of age, the most common ocular adverse events included injection (10.9%), dry eyes (4.5%) and itching (3.6%), but these values were not statistically different when compared with placebo.[80]

4.3 Azelastine

Azelastine, a phthalazinone derivative, is a relatively selective H_1-receptor antagonist and inhibitor of the release of histamine and other mediators from mast cells. It was first shown to be clinically effective in relieving the symptoms of allergic rhinitis following oral or intranasal administration. There are several studies that demonstrate that azelastine is effective in the relief of allergic conjunctivitis.[81-84] Azelastine has been shown *in vitro* to inhibit the release of IL-6, TNFα and IL-8 from mast cells.[85] It appears to be more potent than olopatadine in inhibiting mast cell release of tryptase and IL-6.[86] Also, azelastine downregulates ICAM-1 expression on conjunctival epithelial cells.[87]

4.4 Emedastine

Emedastine is a selective H_1-receptor antagonist. In addition to antihistaminic activity, emedastine appears to possess a potent and selective inhibitory

effect on eosinophils chemotaxis.[88,89] Emedastine has superior H_1-receptor binding affinity when compared with ketotifen, levocabastine, mepyramine, pheniramine, chlorphenamine (chlorpheniramine) or antazoline.[10] It has been found to be more effective than topical levocabastine in reducing and preventing ocular itching associated with allergic conjunctivitis.[90-92] Both emedastine and levocabastine were equivalent in controlling conjunctival hyperaemia, and both were well tolerated. Emedastine was also found to be superior to topical nedocromil in alleviating ocular redness and itching at 3 and 10 minutes after allergen challenge in the conjunctival antigen challenge model.[93] Furthermore, emedastine is superior to topical ketorolac, an NSAID, in controlling ocular itching and redness in the clinical setting of allergic conjunctivitis.[94] When compared with oral loratadine, emedastine was more efficacious in reducing the itching and redness associated with allergic conjunctivitis in the conjunctival antigen challenge model.[95]

4.5 Epinastine

The latest 'multiple-action' topical agent, epinastine, is an H_1- and H_2-receptor antagonist with mast-cell stabilising and anti-inflammatory properties. H_2-receptor antagonism may provide additional benefits in reducing hyperaemia and eyelid swelling. In a small study of ten volunteers, pretreatment with cimetidine, an H_2-receptor antagonist, blocked the vasodilatory effects of an H_2-receptor agonist, which has been shown to increase ocular hyperaemia.[9] This effect is not seen by H_1-receptor antagonism alone, indicating combined H_1- and H_2-receptor antagonism may reduce vasodilation. In a conjunctival antigen challenge study, epinastine has been shown to inhibit eyelid swelling by 72% at 5 minutes after allergen challenge compared with 7% by vehicle placebo.[96] The same study found epinastine to have a rapid onset of action (3 minutes) and a long duration of action (≥8 hours). Epinastine was found to be similar or superior to levocabastine in the relief of ocular itching and hyperaemia.[97,98] Epinastine was shown to be superior to olopatadine in reducing ocular itching in a small conjunctival antigen challenge study.[99] Safety and tolerability of epinastine appear to be equal to that of most other topical antihistamines.

5. Oral versus Topical Treatment

If the allergic symptoms are primarily ocular, then topical treatments appear to be preferred to systemic treatment. Topical agents are superior, with faster onset of action (within minutes) than systemic agents, and, thus, are readily able to retard the allergic response. In head-to-head comparisons, several studies utilising the conjunctival antigen challenge model demonstrated the superiority of topical agents over systemic antihistamines in the treatment of allergic conjunctivitis. Olopatadine was found to be superior to loratadine and fexofenadine.[69,100] Levocabastine was found to be superior to loratadine.[65] Oral antihistamines can offer relief from other symptoms of allergy besides just ocular, but have a delayed onset of action when compared with topical ocular agents.

6. Oral plus Topical Treatment

Combination regimens of an oral second-generation antihistamine and a topical agent have been shown to be superior to oral treatment alone in the conjunctival antigen challenge models. Topical ketotifen used in conjunction with oral desloratadine was more effective in the management of ocular and nasal symptoms of allergic rhinoconjunctivitis than desloratadine alone.[52] In another study, topical olopatadine, in conjunction with oral loratadine, significantly reduced ocular itching at 3, 7 and 10 minutes after allergen challenge, when compared with oral loratadine alone ($p < 0.05$).[101] In a study by Alexander et al.,[102] supplementation of oral fexofenadine therapy with topical nedocromil was found to provide effective control of the ocular component of seasonal allergic rhinoconjunctivitis. Patients were assigned to three treatment groups: (i) fexofenadine 60mg twice daily/nedocromil rescue; (ii) fexofenadine 60mg once daily/nedocromil twice daily; and (iii) fexofenadine rescue/nedocromil twice daily. All three treatment groups significantly reduced the ocular symptoms ($p < 0.003$), but the

latter two groups were the most favourably rated regimens. Superior relief in ocular symptoms is achieved with a regimen in which nedocromil is given as maintenance therapy and fexofenadine is given as either rescue therapy or as maintenance in low dosages.

7. Discussion and Conclusion

There has been an increase of research and development in the area of ocular allergy, but there has also been a large source of information buried in the allergic rhinitis literature as it is more commonly referred to as 'allergic rhinoconjunctivitis'. As the research and development of new therapies concentrated on the treatment of ocular allergy becomes more prominent, the focus of the literature will switch from allergic rhinoconjunctivitis to 'allergic conjunctivorhinitis'.

As monotherapy, oral or systemic antihistamines are an excellent choice when attempting to control multiple early-phase and some late-phase allergic symptoms in the eyes, nose and pharynx. Despite their efficacy in relief of allergic symptoms, systemic antihistamines unfortunately may result in unwanted adverse effects, such as drowsiness and dry mouth. Newer second-generation antihistamines are preferred over older first-generation antihistamines in order to avoid the sedative and anticholinergic effects that are associated with first-generation agents.

When the allergic symptom or complaint is isolated, such as ocular pruritus, focused therapy with topical antihistaminic agents is often efficacious and clearly superior, either as monotherapy or in conjunction with an oral or intranasal agent. Topical antihistaminic agents provide faster and superior relief than systemic antihistamines. Topical antihistaminic agents also possess a longer duration of action than other classes.

Topical vasoconstrictor agents do provide rapid relief especially for redness. However, the relief is often short-lived and overuse of vasoconstrictors may lead to rebound hyperaemia and irritation. Another class of topical agents, mast cell stabilisers, may be considered; however, they generally have a much slower onset of action. The efficacy of mast cell stabilisers may be attributed to anti-inflammatory properties in addition to mast cell stabilisation. One mast cell stabiliser, nedocromil, has also been found to have a neuromodulatory effect. In animal models and *in vitro* studies, nedocromil has been shown to have an inhibitory effect on sensory nerve activation and tachykinin release.[103] Another topical NSAID ketorolac has been promoted for ocular itching, but it has been found to be inferior for relief of allergic conjunctivitis when compared with olopatadine and emedastine.[94,104] Furthermore, topical corticosteroids may be considered for severe seasonal ocular allergy symptoms, although long-term use should be avoided because of the risk of ocular adverse effects, including glaucoma and cataract formation.

In the future there might be a role for topical ciclosporin (cyclosporin) in the treatment of severe allergic conjunctivitis. In several small trials, it has been found to be well tolerated and effective in the therapy of allergic keratoconjunctivitis and vernal keratoconjunctivitis.[105-109] Currently, topical ciclosporin is approved by the US FDA for only one indication: it is indicated to increase tear production in patients whose tear production is suppressed as a result of ocular inflammation associated with keratoconjunctivitis sicca. At present, the role of topical ciclosporin as a steroid-sparing agent in the treatment of allergic conjunctivitis has not been fully investigated.

The armamentarium against rhinoconjunctivitis has continued to expand in recent years with the introduction of newer agents. The newer antihistamines are highly potent. They possess activity beyond selective H_1-receptor inhibition. Many of the selective H_1-receptor antagonists have anti-inflammatory activity, and have become beneficial against the ocular late-phase reaction. Cetirizine, fexofenadine, levocabastine and azelastine have been shown to downregulate ICAM-1 expression in conjunctival epithelial cells. ICAM-1 is a cell adhesion molecule that has been postulated as integral for the homing and migration of leucocytes into inflamed tissue.[110] The downregulation of ICAM-1 expression can

blunt the late-phase reaction, such that the inflammatory cell mucosal infiltration is minimised. With a better understanding of the activities of newer antihistamines, an effective and safe treatment regimen can be offered to all patients with ocular allergy.

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